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Homogenization of oxygen transport in biological tissues

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In this paper, we extend previous work on the mathematical modeling of oxygen transport in biological tissues [23]. Specifically, we include in the modeling process the arterial and venous microstructure within the tissue by means of homogenization techniques. We focus on the two-layer tissue architecture investigated in [23] in the context of abdominal tissue flaps that are commonly used for reconstructive surgery. We apply two-scale convergence methods and unfolding operator techniques to homogenize the developed microscopic model, which involves different unit-cell geometries in the two distinct tissue layers (skin layer and fat tissue) to account for different arterial branching patterns.

Keywords: Oxygen transport; homogenization; two-scale convergence; unfolding method; thin domains; arterial branching pattern; tissue engineering; DIEP tissue flap; reconstructive surgery.

AMS Subject Classifications: 35-XX, 74Q10, 74Q15, 96-XX

1. Introduction

Flow of blood and delivery of oxygen within a tissue is an area of intense research activity [11]. At the larger end of the scale, flows through branching vessels have been studied extensively [5, 31, 32]. At the capillary scale, detailed experimental and simulation studies of flows in the microvasculature have been carried out [13, 24, 30, 33], taking into account such factors as changes in the apparent blood viscosity with vessel diameter, and separation of red blood cells and plasma at bifurcations [20].

A more coarse-grained approach, pursued by several authors, has been to treat blood flow through the vascular network as akin to fluid flow through a porous medium. On a smaller scale, this approach was used by Pozrikidis and Farrow [29] to describe fluid flow within a solid tumor. More recent work by Chapman et al. [7] extended this approach to consider flow through a rectangular grid of capillaries within a tumor, where the interstitium was assumed to be an isotropic porous medium, and Poiseuille flow was assumed in the capillaries. Through the use of formal asymptotic expansions, it was found that on the lengthscale of the tumor (i.e., a lengthscale much longer than the typical capillary separation) the behavior of the capillary bed was also effectively that of a porous medium. A more phenomenological approach was taken by Breward et al. [6], who developed a multiphase model describing vascular tumor growth. Here, the tumor is composed of a mixture of tumor cells, extracellular material, and blood vessels, with the model being used to investigate the impact of angiogenesis or blood vessel occlusion on

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tumor growth. A similar model was used by O'Dea et al. [28] to describe tissue growth in a perfusion bioreactor.

Matzavinos et al. [23] adopted a similar multiphase modeling approach to investigate the transport of oxygen in abdominal tissue flaps, commonly used for plastic and reconstructive surgery. Among existing types of abdominal tissue flaps, the deep inferior epigastric perforator (DIEP) flap is a central component in the current practice of several reconstructive surgical procedures [14]. Nonetheless, complications such as fat necrosis and partial (or even total) tissue flap loss due to poor oxygenation still remain an important concern. Gill et al. [12] reported that in their study of 758 DIEP cases, 12.9 percent of the flaps developed fat necrosis and 5.9 percent of the patients had to return to the operating room. In view of these data, Matzavinos et al. [23] investigated computationally the level of oxygenation in a tissue given its size and shape and the diameters of the perforating arteries. The approach adopted in [23] considered a multiphase mixture of tissue cells, arterial blood vessels, and venous blood vessels, distributed throughout a domain of interest according to specified volume fractions.

In this paper, we improve upon the coarse-grained description of [23] by employing a homogenization approach that takes into account the detailed microstructure of arterial and venous blood vessels. The microscopic model under consideration tracks the flow of blood in a specified geometry of arteries and veins within a tissue flap and the transport of oxygen in arteries, veins, and tissue. A two-layer tissue architecture is adopted that involves different unit-cell geometries (accounting for different arterial branching patterns) in the two distinct tissue layers. We apply a combination of two-scale convergence methods [3, 27] and unfolding operator techniques [8–10] to homogenize the microscopic model. Our main results are Theorems 2.1, 2.2, 2.5 and 2.6 on the macroscopic equations for the blood velocity fields and the oxygen concentrations under different scaling assumptions for the two tissue layers. Moreover, in Theorems 5.3 and 5.6, we generalize to thin domains existing convergence results for the periodic unfolding method.

Derivations of the effective macroscopic equations are important for an accurate numerical simulation of the oxygen distribution in biological tissue. To address different structures of tissues, we consider two different cases which correspond to different scaling regimes: (i) the depth of the skin layer is of the same order as the representative size of the microstructure and (ii) the depth of the skin layer is much larger than the size of the microstructure, but much smaller than the depth of the fat tissue. For both cases we obtain the Darcy law as the macroscopic equation for blood flow in fat tissue. In the skin layer, we reduce the interface at the boundary of the fat tissue layer to two dimensions and obtain the Darcy law with the force term defined by inflow or outflow of blood from the fat tissue layer. We obtain reaction-diffusion-convection and reaction-diffusion equations as macroscopic models for oxygen transport in blood and tissue oxygen concentrations, respectively. The transport of oxygen between tissue and arterial blood on the surface of the blood vessels is represented by the reaction terms in the macroscopic equations. Additionally, in the macroscopic equations for the oxygen concentration in the skin layer, we obtain the source terms defined by the inflow and outflow of oxygen from the fat tissue layer.

The main difference in the results for the two cases is that the unit cell problems are distinct, hence we obtain different effective permeability tensors and diffusion matrices. Thus we obtain different flow velocity and oxygen concentration transport equations depending on the relationship between the thickness of the skin layer and the structure of the blood vessel networks. The macroscopic equations derived

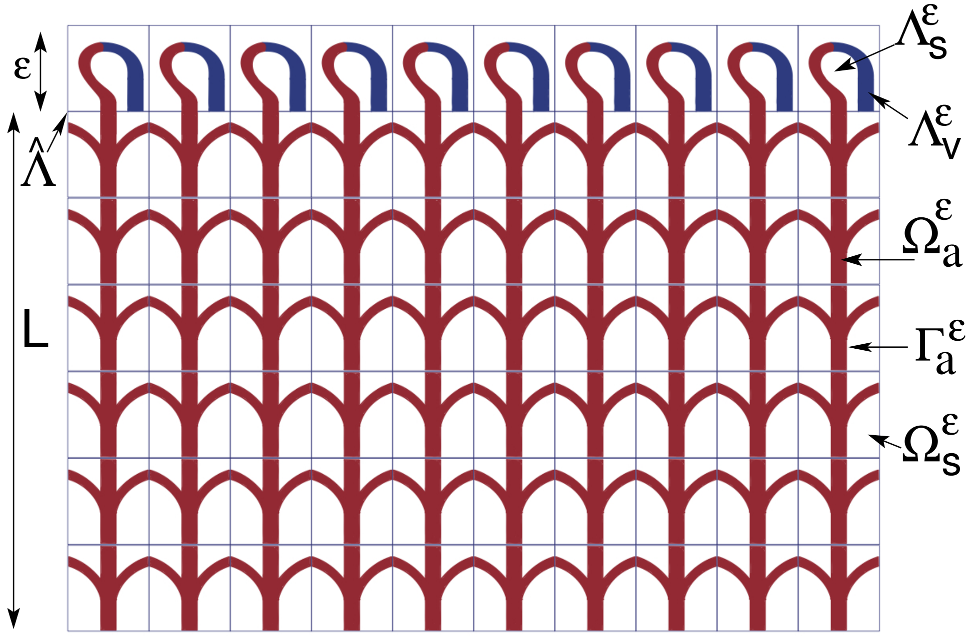

Figure 1. Two dimensional schematic representation of a three-dimensional rectangular domain representing an abdominal tissue flap. The top layer of unit cells (denoted by Λ^ε in the text) corresponds to the dermic and epidermic layers of the skin, whereas the remainder of the domain (denoted by Ω in the text) corresponds to fat tissue. Only the arterial blood vessels are shown in the fat tissue layer. Arteries (in red) and veins (in blue) are shown in the skin tissue layer, which is characterized by the presence of arterial-venous connections, i.e. geometric regions where arteries and veins meet.

from the microscopic description of the processes take into account the microscopic structure of blood vessels network and provide a more realistic model for the oxygen transport in biological tissues.

The literature on the homogenization of fluid flows in porous media is vast (see, e.g., [2, 4, 16, 25, 34] and the references therein). Some representative results in this area are as follows. The macroscopic equations for water flow between two porous media with different porosities were first derived in [19]. A multiscale analysis of the Stokes and Navier-Stokes problems in a thin domain was conducted in [22], where the authors considered applications to lower-dimensional models in fluid mechanics. Various results on the multiscale analysis of reaction-diffusion-convection equations in perforated domains with reactions on the surfaces of the microstructure can be found in [1, 16–18]. Macroscopic equations for elliptic and parabolic reaction-diffusion equations posed in domains separated by a thin perforated layer (e.g., a sieve or a membrane) were derived in [10, 26]. From a mathematical perspective, the novelties of this paper include (a) the analysis of the flow between a fixed-size domain (fat tissue layer) and an ε-thin layer (skin layer) under an appropriate scaling of the transmission conditions, and (b) a different scaling of the reaction-diffusion-convection equations than the one commonly used in the literature (see, e.g., [26]).

The paper is organized as follows. In section 2, we collect the main results of the paper. In section 3, we formulate the microscopic model to be analyzed in the remainder of the paper, initially under the assumption that the depth of the top (skin) layer has the same length scale ε as the unit cell of the fat tissue layer. In section 4, we define the notion of weak solution used in the paper, and in section 5 we provide *a priori* estimates for the solutions of the microscopic model and prove convergence results for the unfolding operator for functions defined in thin domains.

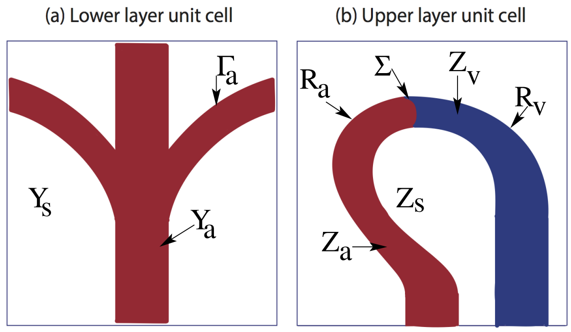

Figure 2. Two-dimensional schematic representation of the two distinct, three-dimensional unit-cell geometries used in the microscopic model: (a) unit-cell geometry corresponding to the lower layer, i.e. the fat tissue layer; (b) unit-cell geometry corresponding to the upper layer, which represents the dermic and epidermic layers of the skin. Only the arterial blood vessels are shown in the fat tissue layer.

These estimates are used in combination with an unfolding operator approach [8–10] to prove the convergence of the solutions of the microscopic equations as $\varepsilon \to 0$. In sections 6 and 7 we derive the homogenized, macroscopic equations for the blood velocity fields (in arteries and veins) and the oxygen concentrations (in arteries, veins, and tissue), respectively. Finally, in section 8, we relax some of the scaling assumptions of the previous sections, and we assume that the depth of the top (skin) layer is of a different length scale than the unit cell of the fat tissue layer.

2. Formulation of the main results

In this section, we collect the main results of the paper. The notation used is further explained in section 3. As discussed in the introduction, we are mainly concerned with the derivation of macroscopic equations for oxygen transport in a two-layer tissue architecture using different scaling assumptions for the distinct layers. The microscopic geometry that leads to the macroscopic models of this section is discussed in sections 3 and 8.

2.1. *Macroscopic coefficients and unit cell problems*

First, we formulate the macroscopic coefficients and the unit cell problems that will be obtained in the derivation of the macroscopic equations. We differentiate between two cases which correspond to skin tissue layers of different relative thicknesses (see section 3 for an explanation of the terms involved).

Case 1

If the thickness of the skin layer (see Fig. 1) is of the same order as the microscopic structure, then the macroscopic permeability matrices $\mathcal{K}_l$ and $\hat{\mathcal{K}}$ for the blood flow are defined by

$$\mathcal{K}_l^{ji} = \frac{1}{|Y|}\int_{Y_l} \omega^i_{l,j}(y)\, dy, \qquad \hat{\mathcal{K}}^{jm} = \frac{1}{|\hat{Z}|}\int_{Z_{av}} \hat{\omega}^m_j(y)\, dy, \tag{1}$$

where ω_l^i and $\hat{\omega}^m$ are solutions of the unit cell problems

$$\begin{cases} -\mu \Delta_y \omega_l^i + \nabla_y \pi_l^i = \mathbf{e}_i, \quad \mathrm{div}_y \, \omega_l^i = 0 \quad \text{in } Y_l, \quad i = 1, \dots, n, \quad l = a, v, \\ \omega_l^i = 0 \qquad \text{on } \Gamma_l, \qquad\qquad \omega_l^i, \ \pi_l^i \quad Y_l - \text{periodic}, \end{cases} \tag{2}$$

and

$$\begin{cases} -\mu \Delta_y \hat{\omega}^m + \nabla_y \hat{\pi}^m = \mathbf{e}_m, & \mathrm{div}_y \, \hat{\omega}^m = 0 \quad \text{in } Z_{av}, \quad m = 1, \dots, n-1, \\ (2\mu S_y \hat{\omega}^m - \hat{\pi}^m I)\mathbf{n} \times \mathbf{n} = 0, & \hat{\omega}^m \cdot \mathbf{n} = 0 \quad \text{on } \hat{Z}_{av}^0, \\ \hat{\omega}^m = 0 \quad \text{on } R_{av} \cup \hat{Z}_{av}^1, & \hat{\omega}^m, \ \hat{\pi}^m \quad \hat{Z} - \text{periodic}. \end{cases} \tag{3}$$

The macroscopic diffusion coefficients $\mathcal{A}_l$ and $\hat{\mathcal{A}}_m$ in the limit equations for the oxygen concentration are given by

$$\begin{aligned} \mathcal{A}_l^{ij} &= \frac{1}{|Y|} \int_{Y_l} \Big[D_l^{ij}(y) + \sum_{k=1}^n D_l^{ik}(y) \frac{\partial w_l^j}{\partial y_k} \Big] dy, \\ \hat{\mathcal{A}}_m^{ij} &= \frac{1}{|\hat{Z}|} \int_{Z_m} \Big[\hat{D}_m^{ij}(y) + \sum_{k=1}^n \hat{D}_m^{ik}(y) \frac{\partial \hat{w}_m^j}{\partial y_k} \Big] dy, \end{aligned} \tag{4}$$

where $l = a, v, s$ and $m = av, s$. The functions w_l and $\hat{w}_m$ are solutions of the unit cell problems

$$\begin{cases} -\mathrm{div}_y (D_l(y)(\nabla_y w_l^j + \mathbf{e}_j)) = 0 & \text{in } Y_l, \quad \text{for } l = a, v, s, \quad j = 1, \dots, n, \\ D_l(y)(\nabla_y w_l^j + \mathbf{e}_j) \cdot \mathbf{n} = 0 & \text{on } \Gamma_l, \quad w_l^j \quad Y - \text{periodic} \end{cases} \tag{5}$$

and

$$\begin{cases} -\mathrm{div}_y (\hat{D}_m(y)(\nabla_y \hat{w}_m^j + \mathbf{e}_j)) = 0 & \text{in } Z_m, \\ \hat{D}_m(y)(\nabla_y \hat{w}_m^j + \mathbf{e}_j) \cdot \mathbf{n} = 0 & \text{on } R_{av}, \ \text{on } \hat{Z}_m^0 \cup \hat{Z}_m^1, \\ \hat{w}_m^j \qquad \hat{Z} - \text{periodic}, & \text{for } m = av, s \ \text{ and } \ j = 1, \dots, n-1. \end{cases} \tag{6}$$

Case 2

If the thickness of the skin layer is (a) considerably larger than the characteristic size of the microscopic structure and (b) significantly smaller than the thickness of the fat tissue layer, then, in the fat tissue layer, the macroscopic permeability tensors $\mathcal{K}_l$, $l = a, v$, and the macroscopic diffusion coefficients $\mathcal{A}_\alpha$, $\alpha = a, v, s$, are identical to those defined in (1) and (4). However, different permeability and diffusion coefficients are obtained for the macroscopic equations describing the blood flow and oxygen transport in the skin layer. Specifically, we obtain

$$\widetilde{\mathcal{K}}^{ji} = \frac{1}{|\widetilde{Z}|} \int_{\widetilde{Z}_{av}} \widetilde{\omega}_j^i(y) dy, \quad \widetilde{\mathcal{A}}_m^{ij} = \frac{1}{|\widetilde{Z}|} \int_{\widetilde{Z}_m} \Big[\hat{D}_m^{ij}(y) + \sum_{k=1}^n \hat{D}_m^{ik}(y) \partial_{y_k} \widetilde{w}_m^j(y) \Big] dy, \tag{7}$$

where $m = av, s$, and $\widetilde{\omega}^i$ and $\widetilde{w}_m^j$ are solutions of the unit cell problems

$$\begin{cases} -\mu\Delta_y\widetilde{\omega}^i + \nabla_y\widetilde{\pi}^i = \mathbf{e}_i, & \mathrm{div}_y\,\widetilde{\omega}^i = 0 \quad \text{in} \quad \widetilde{Z}_{av}, \\ \widetilde{\omega}^i = 0 \quad \text{on} \quad \widetilde{R}_{av}, & \widetilde{\omega}^i,\, \widetilde{\pi}^i \quad \widetilde{Z} - \text{periodic.} \end{cases} \tag{8}$$

and

$$\begin{cases} -\mathrm{div}_y(\hat{D}_m(y)(\nabla_y\widetilde{w}_m^j + \mathbf{e}_j)) = 0 & \text{in } \widetilde{Z}_m, \quad m = av, s, \\ \hat{D}_m(y)(\nabla_y\widetilde{w}_m^j + \mathbf{e}_j)\cdot\mathbf{n} = 0 & \text{on } \widetilde{R}_{av}, \quad \widetilde{w}_m^j \quad \widetilde{Z} - \text{periodic .} \end{cases} \tag{9}$$

2.2. *Macroscopic equations for velocity fields and oxygen concentrations*

Given the definitions of the macroscopic coefficients and the unit cell problems in section 2.1, we are now in a position to state the theorems that are proved in the remainder of the paper. We start by defining the spaces

$$\begin{aligned} &H(\mathrm{div};\Omega) = \{v \in L^2(\Omega)^n,\ \mathrm{div}\, v \in L^2(\Omega)\}, \\ &W(\Omega) = \{w \in H^1(\Omega),\ w = 0 \ \text{ on } \ \Gamma_D\}. \end{aligned}$$

Case 1

The main results of the paper under the scaling assumptions of Case 1, as discussed in section 2.1, are theorems 2.1 and 2.2. These provide the macroscopic equations for the blood velocity fields (in arteries and veins) and oxygen concentrations (in arteries, veins, and tissue) respectively. The notation used in the statements of the theorems is introduced in section 3.

Theorem 2.1 *The sequence of solutions of the microscopic model* (22)–(27) *converges to functions* $\mathbf{v}_l^0 \in H(\mathrm{div};\Omega)$, $p_l - p_l^0 \in W(\Omega)$, $\hat{\mathbf{v}}_{av}^0 \in L^2(\hat{\Lambda})$, *and* $\hat{p} \in H^1(\hat{\Lambda})$ *that satisfy the macroscopic equations*

$$\begin{aligned} &\mathbf{v}_l^0 = -\mathcal{K}_l\nabla p_l, && div\,(\mathcal{K}_l\nabla p_l) = 0 \quad in\ \Omega, \\ &p_l = \hat{p} \qquad on\ \hat{\Lambda}\ , && \\ &p_l = p_l^0 \qquad on\ \Gamma_D, && \mathcal{K}_l\nabla p_l\cdot\mathbf{n} = 0 \quad on\ \partial\hat{\Omega}\times(-L,0), \end{aligned} \tag{10}$$

where $l = a, v$, *and*

$$\begin{aligned} &\hat{\mathbf{v}}_{av}^0 = -2\hat{\mathcal{K}}\nabla_{\hat{x}}\hat{p}, \qquad 2\,div_{\hat{x}}(\hat{\mathcal{K}}\nabla_{\hat{x}}\hat{p}) = \mathcal{K}_a\nabla p_a\cdot\mathbf{n} + \mathcal{K}_v\nabla p_v\cdot\mathbf{n} \quad in\ \hat{\Lambda}, \\ &\hat{\mathcal{K}}\nabla_{\hat{x}}\hat{p}\cdot\mathbf{n} = 0 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad on\ \partial\hat{\Lambda}. \end{aligned} \tag{11}$$

Theorem 2.2 *The sequence of solutions of the microscopic model* (28)–(35) *con-*

verges to a solution of the macroscopic equations

$$
\begin{aligned}
&\theta_l \partial_t c_l - div(\mathcal{A}_l \nabla c_l - \mathbf{v}_l^0 c_l) = \lambda_l \gamma_l (c_s - c_l) && in\ \Omega_T, \\
&\theta_s \partial_t c_s - div(\mathcal{A}_s \nabla c_s) = \sum_{l=a,v} \lambda_l \gamma_l (c_l - c_s) - \theta_s \fint_{Y_s} d_s\, dy\, c_s && in\ \Omega_T, \\
&c_l(t,\hat{x},0) = \hat{c}(t,\hat{x}), \qquad c_s(t,\hat{x},0) = \hat{c}_s(t,\hat{x}) && on\ \hat{\Lambda}_T, \\
&(\mathcal{A}_l \nabla c_l - \mathbf{v}_l^0 c_l)\cdot \mathbf{n} = 0 \qquad on\ (\partial\Omega \setminus (\hat{\Lambda} \cup \Gamma_D)) \times (0,T), \\
&c_l(t,x) = c_{l,D}(t,x) && on\ \Gamma_{D,T}, \\
&\mathcal{A}_s \nabla c_s \cdot \mathbf{n} = 0 \qquad on\ (\partial\Omega \setminus \hat{\Lambda}) \times (0,T), \\
&c_l(0,x) = c_l^0(x), \qquad c_s(0,x) = c_s^0(x) && in\ \Omega,
\end{aligned}
\tag{12}
$$

where $\theta_l = |Y_l|/|Y|$, $\gamma_l = |\Gamma_l|/|Y|$, $l = a, v$, *and* $\theta_s = |Y_s|/|Y|$. *Moreover, in the domain* $\hat{\Lambda}_T$, *we have*

$$
\begin{aligned}
&\hat{\theta}_{av} \partial_t \hat{c} - div_{\hat{x}}(\hat{\mathcal{A}}_{av} \nabla_{\hat{x}} \hat{c} - \hat{\mathbf{v}}_{av}^0\, \hat{c}) = \mathcal{R}_{av}(\hat{c}_s - \hat{c}) - \sum_{l=a,v} (\mathcal{A}_l \nabla c_l - \mathbf{v}_l^0 c_l)\cdot \mathbf{n}, \\
&\hat{\theta}_s \partial_t \hat{c}_s - div_{\hat{x}}(\hat{\mathcal{A}}_s \nabla_{\hat{x}} \hat{c}_s) = \mathcal{R}_{av}(\hat{c} - \hat{c}_s) - \mathcal{A}_s \nabla c_s \cdot \mathbf{n} - \hat{\theta}_s \fint_{Z_s} \hat{d}_s\, dy\, \hat{c}_s, \\
&(\hat{\mathcal{A}}_{av} \nabla_{\hat{x}} \hat{c} - \hat{\mathbf{v}}_{av}^0 \hat{c})\cdot \mathbf{n} = 0 \quad on\ (0,T)\times\partial\hat{\Lambda}, \quad \hat{c}(0,\hat{x}) = \hat{c}^0(\hat{x}) \quad in\ \hat{\Lambda}, \\
&\hat{\mathcal{A}}_s \nabla_{\hat{x}} \hat{c}_s \cdot \mathbf{n} = 0 \quad on\ (0,T)\times\partial\hat{\Lambda}, \quad \hat{c}_s(0,\hat{x}) = \hat{c}_s^0(\hat{x}) \quad in\ \hat{\Lambda},
\end{aligned}
\tag{13}
$$

where $\hat{\theta}_{av} = |Z_{av}|/|\hat{Z}|$, $\hat{\theta}_s = |Z_s|/|\hat{Z}|$, *and* $\mathcal{R}_{av} = \hat{\lambda}_a |R_a|/|\hat{Z}| + \hat{\lambda}_v |R_v|/|\hat{Z}|$. *The macroscopic transport velocities* $\mathbf{v}_l^0$, $\hat{\mathbf{v}}_{av}^0$ *are given by*

$$
\mathbf{v}_l^0(x) = \frac{1}{|Y|}\int_{Y_l} \mathbf{v}_l(x,y)dy, \quad \hat{\mathbf{v}}_{av}^0(\hat{x}) = \frac{1}{|\hat{Z}|}\int_{Z_{av}} \hat{\mathbf{v}}_{av}(\hat{x},y)dy, \quad l = a, v. \tag{14}
$$

The solutions of equations (12)–(13) *satisfy* $c_l - c_{l,D} \in L^2(0,T;W(\Omega)) \cap H^1(0,T;L^2(\Omega))$ *for* $l = a, v$, *and* $c_s \in L^2(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega))$. *Moroever,* $\hat{c}, \hat{c}_s \in L^2(0,T;H^1(\hat{\Lambda})) \cap H^1(0,T;L^2(\hat{\Lambda}))$. *Finally,* $\hat{c}$, $\hat{c}_s \in L^\infty(\hat{\Lambda}_T)$ *and* $c_l \in L^\infty(\Omega_T)$ *for* $l = a, v, s$.

Case 2

If we consider the scaling assumptions of Case 2, then we have to introduce two parameters: a parameter $\varepsilon > 0$ that characterizes the length scale of the microstructure and a parameter $\delta > 0$ that represents the thickness of the skin tissue layer.

We first derive a system of "intermediate" equations by letting $\varepsilon \to 0$ while keeping δ fixed, as follows.

Theorem 2.3 *As* $\varepsilon \to 0$ *the sequence of solutions of the microscopic model given by* (22), (24), (27), *and* (68)–(70) *converges to functions* $\overline{\mathbf{v}}_l^\delta \in H(\mathrm{div};\Omega)$, $p_l^\delta - p_l^0 \in W(\Omega)$, $\widetilde{\mathbf{v}}_{av}^\delta \in H(\mathrm{div};\Lambda_\delta)$, *and* $\hat{p}^\delta \in H^1(\Lambda_\delta)$, *respectively, with* $l = a, v$, *that satisfy* *the macroscopic model*

$$
\begin{aligned}
&\overline{\mathbf{v}}_l^\delta = -\mathcal{K}_l \nabla p_l^\delta, && div(\mathcal{K}_l \nabla p_l^\delta) = 0 && in\ \ \Omega,\\
&\widetilde{\mathbf{v}}_{av}^\delta = -\widetilde{\mathcal{K}} \nabla \hat{p}^\delta, && div(\widetilde{\mathcal{K}} \nabla \hat{p}^\delta) = 0 && in\ \ \Lambda_\delta,\\
&\mathcal{K}_v \nabla p_v^\delta \cdot \mathbf{n} + \mathcal{K}_a \nabla p_a^\delta \cdot \mathbf{n} = \frac{1}{\delta} \widetilde{\mathcal{K}} \nabla \hat{p}^\delta \cdot \mathbf{n}, && p_l^\delta = \hat{p}^\delta && on\ \ \hat{\Lambda}\ ,\\
&\mathcal{K}_l \nabla p_l^\delta \cdot \mathbf{n} = 0 \quad on\ \ \partial\Omega \setminus (\Gamma_D \cup \hat{\Lambda})\ , && p_l^\delta = p_l^0 && on\ \ \Gamma_D,\\
&\widetilde{\mathcal{K}} \nabla \hat{p}^\delta \cdot \mathbf{n} = 0 \quad on\ \ \partial\Lambda_\delta \setminus \hat{\Lambda}.
\end{aligned}
\tag{15}
$$

Theorem 2.4 *As $\varepsilon \to 0$ the sequence of solutions of the microscopic equations (28)–(35) with δ instead of ε in the transmission conditions converges to functions $c_l^\delta - c_{l,D} \in L^2(0,T; W(\Omega))$, $c_s^\delta \in L^2(0,T; H^1(\Omega))$, $c_l^\delta \in H^1(0,T; L^2(\Omega))$, and $\hat{c}_j^\delta \in L^2(0,T; H^1(\Lambda_\delta)) \cap H^1(0,T; L^2(\Lambda_\delta))$ that satisfy the macroscopic problem*

$$
\begin{aligned}
&\theta_l \partial_t c_l^\delta - div(\mathcal{A}_l \nabla c_l^\delta - \overline{\mathbf{v}}_l^\delta c_l^\delta) = \lambda_l \gamma_l (c_s^\delta - c_l^\delta), && in\ \Omega_T,\\
&\widetilde{\theta}_{av} \partial_t \hat{c}_{av}^\delta - div(\widetilde{\mathcal{A}}_{av} \nabla \hat{c}_{av}^\delta - \widetilde{\mathbf{v}}_{av}^\delta \hat{c}_{av}^\delta) = \mathcal{R}_{av}(\hat{c}_s^\delta - \hat{c}_{av}^\delta), && in\ \Lambda_{\delta,T},\\
&c_l^\delta = \hat{c}_{av}^\delta, \qquad \sum_{l=a,v} (\mathcal{A}_l \nabla c_l^\delta - \overline{\mathbf{v}}_l^\delta c_l^\delta) \cdot \mathbf{n} = \frac{1}{\delta} (\widetilde{\mathcal{A}}_{av} \nabla \hat{c}_{av}^\delta - \widetilde{\mathbf{v}}_{av}^\delta \hat{c}_{av}^\delta) \cdot \mathbf{n} && on\ \hat{\Lambda}_T,\\
&(\mathcal{A}_l \nabla c_l^\delta - \overline{\mathbf{v}}_l^\delta c_l^\delta) \cdot \mathbf{n} = 0 \qquad on\ (\partial\Omega \setminus (\hat{\Lambda} \cup \Gamma_D)) \times (0,T),\\
&c_l^\delta = c_{l,D} \qquad on\ \Gamma_D \times (0,T),\\
&(\widetilde{\mathcal{A}}_{av} \nabla \hat{c}_{av}^\delta - \widetilde{\mathbf{v}}_{av}^\delta \hat{c}_{av}^\delta) \cdot \mathbf{n} = 0 \qquad on\ (\partial\Lambda_\delta \setminus \hat{\Lambda}) \times (0,T),\\
&c_l^\delta(0,x) = c_l^0(x) \quad in\ \Omega, \qquad \hat{c}_{av}^\delta(0,x) = \hat{c}^{\delta,0}(x) && in\ \Lambda_\delta,
\end{aligned}
\tag{16}
$$

where $l = a, v$ and $j = av, s$, and

$$
\begin{aligned}
&\theta_s \partial_t c_s^\delta - div(\mathcal{A}_s \nabla c_s^\delta) = \sum_{l=a,v} \lambda_l \gamma_l (c_l^\delta - c_s^\delta) - \theta_s \fint_{Y_s} d_s dy\, c_s^\delta && in\ \Omega_T,\\
&\widetilde{\theta}_s \partial_t \hat{c}_s^\delta - div(\widetilde{\mathcal{A}}_s \nabla \hat{c}_s^\delta) = \mathcal{R}_{av}(\hat{c}_{av}^\delta - \hat{c}_s^\delta) - \widetilde{\theta}_s \fint_{\widetilde{Z}_s} \hat{d}_s dy\, \hat{c}_s^\delta && in\ \Lambda_{\delta,T},\\
&c_s^\delta = \hat{c}_s^\delta, \qquad \mathcal{A}_s \nabla c_s^\delta \cdot \mathbf{n} = \frac{1}{\delta} \widetilde{\mathcal{A}}_s \nabla \hat{c}_s^\delta \cdot \mathbf{n} && on\ \hat{\Lambda}_T,\\
&\mathcal{A}_s \nabla c_s^\delta \cdot \mathbf{n} = 0 \quad on\ (\partial\Omega \setminus \hat{\Lambda}) \times (0,T), \qquad c_s^\delta(0,x) = c_s^0(x) && in\ \Omega,\\
&\widetilde{\mathcal{A}}_s \nabla \hat{c}_s^\delta \cdot \mathbf{n} = 0 \quad on\ (\partial\Lambda_\delta \setminus \hat{\Lambda}) \times (0,T), \qquad \hat{c}_s^\delta(0,x) = \hat{c}_s^{\delta,0}(x) && in\ \Lambda_\delta.
\end{aligned}
\tag{17}
$$

Here the following notation has been used:

$$
\widetilde{\theta}_m = \frac{|\widetilde{Z}_m|}{|\widetilde{Z}|},\ m = av, s,\ \theta_l = \frac{|Y_l|}{|Y|},\ \mathcal{R}_{av} = \frac{\hat{\lambda}_v |\widetilde{R}_v| + \hat{\lambda}_a |\widetilde{R}_a|}{|\widetilde{Z}|},\ \gamma_l = \frac{|\Gamma_l|}{|Y|},\ l = a, v, s,
$$

and the macroscopic transport velocities are defined as

$$
\overline{\mathbf{v}}_l^\delta(x) = \frac{1}{|Y|} \int_{Y_l} \mathbf{v}_l^\delta(x,y)\, dy, \quad \widetilde{\mathbf{v}}_{av}^\delta(x) = \frac{1}{|\widetilde{Z}|} \int_{\widetilde{Z}_{av}} \hat{\mathbf{v}}_{av}^\delta(x,y)\, dy, \qquad l = a, v. \tag{18}
$$

Given these "intermediate" results, we derive the final macroscopic equations by letting $\delta \to 0$ in (15), as follows.

THEOREM 2.5 *As $\delta \to 0$ the sequence of solutions of the equations* (15) *converges to functions $\overline{\mathbf{v}}_l \in H(\mathrm{div};\Omega)$, $p_l - p_l^0 \in W(\Omega)$, $\widetilde{\mathbf{v}}_{av} \in L^2(\hat{\Lambda})$, and $\hat{p} \in H^1(\hat{\Lambda})$, respectively, with $l = a, v$, that satisfy the problem*

$$\begin{aligned}
&\overline{\mathbf{v}}_l = -\mathcal{K}_l \nabla p_l, && div(\mathcal{K}_l \nabla p_l) = 0 && && in\ \ \Omega, \\
&p_l(\hat{x}, 0) = \hat{p}(\hat{x}) && on\ \ \hat{\Lambda}, && p_l = p_l^0 && on\ \ \Gamma_D, \\
&\widetilde{\mathbf{v}}_{av} = -\widetilde{\mathcal{K}} \nabla_{\hat{x}} \hat{p}, && div_{\hat{x}}(\widetilde{\mathcal{K}} \nabla_{\hat{x}} \hat{p}) = \mathcal{K}_a \nabla p_a \cdot \mathbf{n} + \mathcal{K}_v \nabla p_v \cdot \mathbf{n} && && on\ \ \hat{\Lambda}, \\
&\mathcal{K}_l \nabla p_l \cdot \mathbf{n} = 0 && on\ \ \partial\Omega \setminus (\Gamma_D \cup \hat{\Lambda}), && \widetilde{\mathcal{K}} \nabla_{\hat{x}} \hat{p} \cdot \mathbf{n} = 0 && on\ \ \partial\hat{\Lambda}.
\end{aligned} \tag{19}$$

THEOREM 2.6 *As $\delta \to 0$ we obtain the macroscopic problem*

$$\begin{aligned}
&\theta_l \partial_t c_l - div(\mathcal{A}_l \nabla c_l - \overline{\mathbf{v}}_l c_l) = \lambda_l \gamma_l (c_s - c_l), && && in\ \Omega_T\ , \\
&\theta_s \partial_t c_s - div(\mathcal{A}_s \nabla c_s) = \sum_{l=a,v} \lambda_l \gamma_l (c_l - c_s) - \theta_s \fint_{Y_s} d_s(t,y) dy\ c_s && && in\ \Omega_T, \\
&c_l(t, \hat{x}, 0) = \hat{c}_{av}(t, \hat{x}) && c_s(t, \hat{x}, 0) = \hat{c}_s(t, \hat{x}) && on\ \hat{\Lambda}_T, \\
&(\mathcal{A}_l \nabla c_l - \overline{\mathbf{v}}_l c_l) \cdot \mathbf{n} = 0 && on\ (\partial\Omega \setminus (\hat{\Lambda} \cup \Gamma_D)) \times (0, T)\ , \\
&c_l(t, x) = c_{l,D} && && on\ \Gamma_{D,T}, \\
&\mathcal{A}_s \nabla c_s \cdot \mathbf{n} = 0 && on\ (\partial\Omega \setminus \hat{\Lambda}) \times (0, T), \\
&c_l(0, x) = c_l^0(x) && c_s(0, x) = c_s^0(x) && in\ \Omega,
\end{aligned} \tag{20}$$

where $l = a, v$, and in $\hat{\Lambda}_T$ we have

$$\begin{aligned}
&\widetilde{\theta}_{av} \partial_t \hat{c}_{av} - div_{\hat{x}}(\widetilde{\mathcal{A}}_{av} \nabla \hat{c}_{av} - \widetilde{\mathbf{v}}_{av} \hat{c}_{av}) = \mathcal{R}_{av}(\hat{c}_s - \hat{c}_{av}) - \sum_{l=a,v} (\mathcal{A}_l \nabla c_l - \overline{\mathbf{v}}_l c_l) \cdot \mathbf{n}, \\
&\widetilde{\theta}_s \partial_t \hat{c}_s - div_{\hat{x}}(\widetilde{\mathcal{A}}_s \nabla \hat{c}_s) = \mathcal{R}_{av}(\hat{c}_{av} - \hat{c}_s) - \mathcal{A}_s \nabla c_s \cdot \mathbf{n} - \widetilde{\theta}_s \fint_{\widetilde{Z}_s} \hat{d}_s(t,y) dy\ \hat{c}_s, \\
&(\widetilde{\mathcal{A}}_{av} \nabla \hat{c}_{av} - \widetilde{\mathbf{v}}_{av} \hat{c}_{av}) \cdot \mathbf{n} = 0, \qquad \widetilde{\mathcal{A}}_s \nabla \hat{c}_s \cdot \mathbf{n} = 0 \qquad on\ \partial\hat{\Lambda}_T\ , \\
&\hat{c}_{av}(0, \hat{x}) = \hat{c}^0(\hat{x}) \qquad \hat{c}_s(0, \hat{x}) = \hat{c}_s^0(\hat{x}) \qquad in\ \hat{\Lambda}.
\end{aligned} \tag{21}$$

Moreover, the solutions of equations (20) *and* (21) *satisfy $c_l - c_{l,D} \in L^2(0,T;W(\Omega))$, $c_s \in L^2(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega))$, $c_l \in H^1(0,T;L^2(\Omega))$, $\hat{c}_j \in L^2(0,T;H^1(\hat{\Lambda})) \cap H^1(0,T;L^2(\hat{\Lambda}))$ for $l = a, v$, $j = av, s$.*

We remark that the structure of the macroscopic equations for the blood velocity fields is the same in both cases, i.e. in Theorem 2.1 and Theorem 2.5. However, the permeability tensors for the flow in the skin layer are different, since they are determined by solutions of different unit cell problems; see equations (2), (3), and (8). These results reflect the differences in the microscopic structure and the microscopic equations for the skin layer in the two different cases. We also remark that the factor of 2 in the macroscopic equations (11) is specific to Case 1.

A similar situation appears in the macroscopic equations for oxygen transport.

In both cases, we obtain the same structure for the equations; see Theorem 2.2 and Theorem 2.6. However, the macroscopic diffusion coefficients and transport velocities are different, as manifested by equations (4) and (7) for the diffusion coefficients and equations (14) and (18) for the transport velocities. Again, these results reflect the differences in the microscopic structure of the the skin tissue layer in the two different cases.

Finally, the "intermediate" system obtained in Case 2, when we let $\varepsilon \to 0$ but keep δ fixed, represents the macroscopic equations for the blood flow and oxygen concentration in the two domains with different microscopic structures (skin layer and fat tissue layer).

3. The microscopic model

We now introduce the microscopic model that leads to the asymptotic (macroscopic) results stated in the previous section. As in [23] we adopt a three-dimensional rectangular geometry for a DIEP tissue flap with a two-layer tissue architecture. The approach in this paper differs from that in [23] in that the geometry of the vascular microstructure is explicitly defined. A two-dimensional schematic representation of the three-dimensional geometry used is shown in Fig. 1. The top layer of unit cells in Fig. 1 corresponds to the dermic and epidermic layers of the skin, whereas the remainder of the domain corresponds to fat tissue.

We denote the fat tissue layer by $\Omega = \hat{\Omega} \times (-L, 0)$, with some $L > 0$ and $\hat{\Omega} \subset \mathbb{R}^2$. The top (skin) layer is assumed to be thin as compared to the fat tissue layer and is denoted by $\Lambda^\varepsilon = \hat{\Omega} \times (0, \varepsilon)$ with $\Lambda^1 = \hat{\Omega} \times (0, 1)$, $\hat{\Lambda} = \hat{\Omega} \times \{0\}$. The small positive parameter ε represents both the scale of the unit cell describing the arterial branching pattern and the depth of the skin layer (this assumption is relaxed in section 8).

The vascular microstructure is assumed to differ in the two layers of the domain. Specifically, Ω is constructed by a periodic arrangement of a (scaled) unit cell $\overline{Y} = \overline{Y}_a \cup \overline{Y}_v \cup \overline{Y}_s$, where Y_a, Y_v, and Y_s partition Y into the geometric domains of arteries, veins, and tissue, respectively. Figure 2(a) shows an example of such a unit cell that represents a specific arterial branching pattern for the fat tissue layer. We define the domains occupied by arteries, veins and tissue in Ω as $\Omega_a^\varepsilon = \mathrm{Int}\big(\cup_{\xi \in \mathbb{Z}^3} \varepsilon(\overline{Y}_a + \xi)\big) \cap \Omega$, $\Omega_v^\varepsilon = \mathrm{Int}\big(\cup_{\xi \in \mathbb{Z}^3} \varepsilon(\overline{Y}_v + \xi)\big) \cap \Omega$, and $\Omega_s^\varepsilon = \mathrm{Int}\big(\cup_{\xi \in \mathbb{Z}^3} \varepsilon(\overline{Y}_s + \xi)\big) \cap \Omega$, respectively. The small parameter ε corresponds to the size of the arterial microscopic structure. In particular, ε is the ratio between the size of the periodically repeating unit cell and the size of the whole tissue domain.

Similarly, we define a (different) unit cell $\overline{Z} = \overline{Z}_a \cup \overline{Z}_v \cup \overline{Z}_s$ that describes the arterial and venous geometry in Λ^ε. We define $\Lambda_a^\varepsilon = \mathrm{Int}\big(\cup_{\eta \in \mathbb{Z}^2} \varepsilon(\overline{Z}_a + (\eta, 0))\big) \cap \Lambda^\varepsilon$, $\Lambda_v^\varepsilon = \mathrm{Int}\big(\cup_{\eta \in \mathbb{Z}^2} \varepsilon(\overline{Z}_v + (\eta, 0))\big) \cap \Lambda^\varepsilon$, and $\Lambda_s^\varepsilon = \mathrm{Int}\big(\cup_{\eta \in \mathbb{Z}^2} \varepsilon(\overline{Z}_s + (\eta, 0))\big) \cap \Lambda^\varepsilon$ as the domains in Λ^ε of arteries, veins, and tissue respectively. Figure 2(b) shows an example of a unit cell for Λ^ε. Throughout the paper, it is assumed that the skin layer Λ^ε is characterized by the presence of arterial-venous connections that facilitate the exchange of blood between the arterial and venous systems (see, e.g., [15, 23]). A simple example of an arterial-venous connection is shown in Fig. 2(b)

We first consider that the depth of the skin layer is of order ε. This condition is later modified in section 8. In the arteries and veins located in Ω, blood is assumed to flow with velocities $\mathbf{v}_a^\varepsilon(x)$ and $\mathbf{v}_v^\varepsilon(x)$, respectively, according to the Stokes equation with zero-slip boundary conditions. Specifically, we let $p_a^\varepsilon(x)$ and $p_v^\varepsilon(x)$ denote the arterial and venous pressures, respectively, and we assume that

Table 1. Macroscopic domains (see text for details)

Notation	Description
$\Omega = \hat{\Omega} \times (-L, 0)$	Fat tissue layer
$\hat{\Lambda} = \hat{\Omega} \times \{0\}$	Upper boundary of Ω
$\Lambda^\varepsilon = \hat{\Omega} \times (0, \varepsilon)$	Skin layer (scaling of section 3)
$\Lambda_\delta = \hat{\Omega} \times (0, \delta)$	Skin layer (scaling of section 8)

Table 2. Unit cell domains (see text for details)

Notation	Description
$\overline{Y} = \overline{Y}_a \cup \overline{Y}_v \cup \overline{Y}_s$	Unit cell for Ω
$Y_a, Y_v, Y_s \subset Y$	Open subsets with Lipschitz boundaries Γ_a and Γ_v, $Y_a \cap Y_v = \emptyset$
$\overline{Z} = \overline{Z}_a \cup \overline{Z}_v \cup \overline{Z}_s$	Unit cell for Λ^ε
$Z_a, Z_v, Z_s \subset Z$	Open subsets with Lipschitz boundaries R_a and R_v, $Z_a \cap Z_v = \emptyset$
$\overline{\widetilde{Z}} = \overline{\widetilde{Z}}_a \cup \overline{\widetilde{Z}}_v \cup \overline{\widetilde{Z}}_s$	Unit cell for Λ_δ
$\widetilde{Z}_a, \widetilde{Z}_v, \widetilde{Z}_s \subset \widetilde{Z}$	Open subsets with Lipschitz boundaries $\widetilde{R}_a$ and $\widetilde{R}_v$, $\widetilde{Z}_a \cap \widetilde{Z}_v = \emptyset$

$(\mathbf{v}_a^\varepsilon, p_a^\varepsilon)$ and $(\mathbf{v}_v^\varepsilon, p_v^\varepsilon)$ satisfy

$$\begin{cases} -\varepsilon^2 \mu \, \Delta \mathbf{v}_l^\varepsilon + \nabla p_l^\varepsilon = 0 \, , \qquad \operatorname{div} \mathbf{v}_l^\varepsilon = 0 & \text{in } \Omega_l^\varepsilon, \\ \mathbf{v}_l^\varepsilon = 0 & \text{on } \Gamma_l^\varepsilon, \end{cases} \tag{22}$$

where $l = a, v$, and Γ_a^ε and Γ_v^ε denote the outer surface of arteries and veins, respectively, in Ω. As usual, the scaling in the viscosity term is such that the velocity field has a non-trivial limit as $\varepsilon \to 0$ (see, e.g., [16]). Similarly, we assume that in the skin tissue layer Λ^ε, $(\hat{\mathbf{v}}_a^\varepsilon, \hat{p}_a^\varepsilon)$ and $(\hat{\mathbf{v}}_v^\varepsilon, \hat{p}_v^\varepsilon)$ satisfy

$$\begin{cases} -\varepsilon^2 \mu \, \Delta \hat{\mathbf{v}}_l^\varepsilon + \nabla \hat{p}_l^\varepsilon = 0 \, , \quad \operatorname{div} \hat{\mathbf{v}}_l^\varepsilon = 0 & \text{in } \Lambda_l^\varepsilon, \\ \hat{\mathbf{v}}_l^\varepsilon = 0 & \text{on } R_l^\varepsilon \, , \end{cases} \tag{23}$$

where $l = a, v$, and R_a^ε and R_v^ε denote the outer surface of arteries and veins, respectively, in Λ^ε. We define $\partial\Omega = \Gamma_D \cup (\partial\hat{\Omega} \times (-L, 0)) \cup \hat{\Lambda}$, where Γ_D denotes the lower horizontal boundary of the fat tissue layer, and impose the boundary conditions

$$p_l^\varepsilon = p_l^0, \;\; \mathbf{v}_l^\varepsilon \times \mathbf{n} = 0 \;\; \text{ on } \Gamma_D \cap \partial\Omega_l^\varepsilon, \qquad \mathbf{v}_l^\varepsilon = 0 \;\; \text{ on } (\partial\hat{\Omega} \times (-L, 0)) \cap \partial\Omega_l^\varepsilon, \tag{24}$$

where $l = a, v$. We consider Dirichlet boundary conditions for the blood velocities on $\partial\Lambda^\varepsilon = (\partial\hat{\Omega} \times (0, \varepsilon)) \cup \hat{\Lambda} \cup (\hat{\Omega} \times \{\varepsilon\})$

$$\hat{\mathbf{v}}_l^\varepsilon = 0 \quad \text{on } \partial\hat{\Omega} \times (0, \varepsilon) \cap \partial\Lambda_l^\varepsilon, \qquad \hat{\mathbf{v}}_l^\varepsilon = 0 \quad \text{on } \hat{\Omega} \times \{\varepsilon\} \cap \partial\Lambda_l^\varepsilon, \qquad l = a, v, \tag{25}$$

Table 3. Microscopic domains (see text for details)

Notation	Description
$\Omega_a^\varepsilon = \mathrm{Int}\Big(\bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\overline{Y}_a+\xi)\Big)\cap\Omega$	Arteries in fat tissue layer
$\Omega_v^\varepsilon = \mathrm{Int}\Big(\bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\overline{Y}_v+\xi)\Big)\cap\Omega$	Veins in fat tissue layer
$\Omega_s^\varepsilon = \mathrm{Int}\Big(\bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\overline{Y}_s+\xi)\Big)\cap\Omega$	Tissue domain
$\Lambda_a^\varepsilon = \mathrm{Int}\Big(\bigcup_{\eta\in\mathbb{Z}^2} \varepsilon(\overline{Z}_a+(\eta,0))\Big)\cap\Lambda^\varepsilon$	Arteries in skin layer (section 3)
$\Lambda_v^\varepsilon = \mathrm{Int}\Big(\bigcup_{\eta\in\mathbb{Z}^2} \varepsilon(\overline{Z}_v+(\eta,0))\Big)\cap\Lambda^\varepsilon$	Veins in skin layer (section 3)
$\Lambda_s^\varepsilon = \mathrm{Int}\Big(\bigcup_{\eta\in\mathbb{Z}^2} \varepsilon(\overline{Z}_s+(\eta,0))\Big)\cap\Lambda^\varepsilon$	Tissue in skin layer (section 3)
$\Lambda_a^\delta = \mathrm{Int}\Big(\bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\overline{\widetilde{Z}}_a+\xi)\Big)\cap\Lambda_\delta$	Arteries in skin layer (section 8)
$\Lambda_v^\delta = \mathrm{Int}\Big(\bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\overline{\widetilde{Z}}_v+\xi)\Big)\cap\Lambda_\delta$	Veins in skin layer (section 8)
$\Lambda_s^\delta = \mathrm{Int}\Big(\bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\overline{\widetilde{Z}}_s+\xi)\Big)\cap\Lambda_\delta$	Tissue domain in skin layer (section 8)

Table 4. Microscopic boundaries (see text for details)

Notation	Description
$\Gamma_a^\varepsilon = \bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\Gamma_a+\xi)\cap\Omega$	Boundaries of arteries in fat tissue layer
$\Gamma_v^\varepsilon = \bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\Gamma_v+\xi)\cap\Omega$	Boundaries of veins in fat tissue layer
$R_a^\varepsilon = \bigcup_{\eta\in\mathbb{Z}^2} \varepsilon(R_a+(\eta,0))\cap\Lambda^\varepsilon$	Boundaries of arteries in skin layer (section 3)
$R_v^\varepsilon = \bigcup_{\eta\in\mathbb{Z}^2} \varepsilon(R_v+(\eta,0))\cap\Lambda^\varepsilon$	Boundaries of veins in skin layer (section 3)
$\widetilde{R}_a^\varepsilon = \bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\widetilde{R}_a+\xi)\cap\Lambda_\delta$	Boundaries of arteries in skin layer (section 8)
$\widetilde{R}_v^\varepsilon = \bigcup_{\xi\in\mathbb{Z}^3} \varepsilon(\widetilde{R}_v+\xi)\cap\Lambda_\delta$	Boundaries of veins in skin layer (section 8)

and we impose transmission conditions on $\hat{\Lambda}$:

$$\begin{cases} (-2\,\varepsilon^2\mu\,\mathrm{S}\mathbf{v}_l^\varepsilon + p_l^\varepsilon I)\cdot\mathbf{n} = (-2\,\varepsilon^2\mu\,\mathrm{S}\hat{\mathbf{v}}_l^\varepsilon + \hat{p}_l^\varepsilon I)\cdot\mathbf{n} & \text{on } \partial\Omega_l^\varepsilon\cap\hat{\Lambda}\,, \\ \mathbf{v}_l^\varepsilon = \frac{1}{\varepsilon}\hat{\mathbf{v}}_l^\varepsilon & \text{on } \partial\Omega_l^\varepsilon\cap\hat{\Lambda}\,, \end{cases} \tag{26}$$

where $l = a, v$, and $\mathrm{S}\mathbf{u}$ denotes the symmetric gradient $\mathrm{S}\mathbf{u} = 1/2(\partial_{x_i}u_j + \partial_{x_j}u_i)_{ij}$. The ε^{-1} scaling in the velocity boundary condition balances the blood velocity field in the skin layer with the depth of the layer.

We let Σ^ε denote the arterial-venous connections in Λ^ε. In other words, Σ^ε denotes the $n-1$-dimensional surfaces, where arteries and veins meet in $\Lambda^\varepsilon \subset \mathbb{R}^n$. We impose continuity conditions for blood velocities and forces on Σ^ε, as follows.

$$\begin{cases} (-2\varepsilon^2\mu\, \mathrm{S}\hat{\mathbf{v}}_a^\varepsilon + \hat{p}_a^\varepsilon I)\cdot \mathbf{n} = (-2\varepsilon^2\mu\, \mathrm{S}\hat{\mathbf{v}}_v^\varepsilon + \hat{p}_v^\varepsilon I)\cdot \mathbf{n} & \text{on } \Sigma^\varepsilon, \\ \hat{\mathbf{v}}_a^\varepsilon = \hat{\mathbf{v}}_v^\varepsilon & \text{on } \Sigma^\varepsilon\ . \end{cases} \tag{27}$$

The oxygen concentrations in the tissue and the arterial and venous blood within the fat tissue layer are denoted by $c_s^\varepsilon(x,t)$, $c_a^\varepsilon(x,t)$, and $c_v^\varepsilon(x,t)$, respectively. Similarly, the corresponding concentrations in the skin tissue layer are denoted by $\hat{c}_s^\varepsilon(x,t)$, $\hat{c}_a^\varepsilon(x,t)$, and $\hat{c}_v^\varepsilon(x,t)$, respectively. Oxygen in the blood is transported by the flow and diffuses within the fluid. Hence, the equations describing oxygen transport in the blood are given by

$$\begin{cases} \partial_t c_l^\varepsilon - \mathrm{div}(D_l^\varepsilon \nabla c_l^\varepsilon - \mathbf{v}_l^\varepsilon c_l^\varepsilon) = 0 & \text{in } \Omega_l^\varepsilon \times (0,T)\ , \\ \frac{1}{\varepsilon}\partial_t \hat{c}_l^\varepsilon - \frac{1}{\varepsilon}\mathrm{div}(\hat{D}_l^\varepsilon \nabla \hat{c}_l^\varepsilon - \hat{\mathbf{v}}_l^\varepsilon \hat{c}_l^\varepsilon) = 0 & \text{in } \Lambda_l^\varepsilon \times (0,T)\ , \end{cases} \tag{28}$$

where $l = a, v$. Oxygen diffuses within the tissue with diffusion coefficient D_s^ε, and it is assumed to decay and/or be consumed by the tissue cells at a rate proportional to oxygen concentration. The equations for $c_s^\varepsilon(x,t)$ and $\hat{c}_s^\varepsilon(x,t)$ are then

$$\begin{cases} \partial_t c_s^\varepsilon - \mathrm{div}(D_s^\varepsilon \nabla c_s^\varepsilon) = -d_s^\varepsilon c_s^\varepsilon & \text{in } \Omega_s^\varepsilon \times (0,T)\ , \\ \frac{1}{\varepsilon}\partial_t \hat{c}_s^\varepsilon - \frac{1}{\varepsilon}\mathrm{div}(\hat{D}_s^\varepsilon \nabla \hat{c}_s^\varepsilon) = -\frac{1}{\varepsilon}\hat{d}_s^\varepsilon \hat{c}_s^\varepsilon & \text{in } \Lambda_s^\varepsilon \times (0,T)\ . \end{cases} \tag{29}$$

The boundary conditions on the surface of the blood vessels describe the flux of oxygen from the blood into the tissue at a rate proportional to the difference in the oxygen concentrations.

$$\begin{cases} (D_l^\varepsilon \nabla c_l^\varepsilon - \mathbf{v}^\varepsilon c_l^\varepsilon)\cdot \mathbf{n} = -\varepsilon\lambda_l(c_l^\varepsilon - c_s^\varepsilon) & \text{on } \Gamma_l^\varepsilon \times (0,T), \\ (\hat{D}_l^\varepsilon \nabla \hat{c}_l^\varepsilon - \hat{\mathbf{v}}_l^\varepsilon \hat{c}_l^\varepsilon)\cdot \mathbf{n} = -\varepsilon\hat{\lambda}_l(\hat{c}_l^\varepsilon - \hat{c}_s^\varepsilon) & \text{on } R_l^\varepsilon \times (0,T), \end{cases} \tag{30}$$

for $l = a, v$, and

$$\begin{cases} D_s^\varepsilon \nabla c_s^\varepsilon \cdot \mathbf{n} = \varepsilon\lambda_l(c_l^\varepsilon - c_s^\varepsilon) & \text{on } \Gamma_l^\varepsilon \times (0,T), \\ \hat{D}_s^\varepsilon \nabla \hat{c}_s^\varepsilon \cdot \mathbf{n} = \varepsilon\hat{\lambda}_l(\hat{c}_l^\varepsilon - \hat{c}_s^\varepsilon) & \text{on } R_l^\varepsilon \times (0,T), \end{cases} \tag{31}$$

where the constants λ_l and $\hat{\lambda}_l$, $l = a, v$, are the oxygen permeability coefficients of the arterial and venous blood vessels.

In addition to the exchange of oxygen between blood vessels and tissue, oxygen in arterial blood is transported to the venous system through the arterial-venous connections in the upper (skin) layer of the domain. In the following, we assume continuity of concentrations and fluxes at the arterial-venous connections Σ^ε

$$\hat{c}_a^\varepsilon = \hat{c}_v^\varepsilon, \quad (\hat{D}_a^\varepsilon \nabla \hat{c}_a^\varepsilon - \hat{\mathbf{v}}_a^\varepsilon \hat{c}_a^\varepsilon)\cdot \mathbf{n} = (\hat{D}_v^\varepsilon \nabla \hat{c}_v^\varepsilon - \hat{\mathbf{v}}_v^\varepsilon \hat{c}_v^\varepsilon)\cdot \mathbf{n} \quad \text{on } \Sigma^\varepsilon \times (0,T) \tag{32}$$

We also impose transmission conditions between the fat tissue layer and the skin layer

$$\begin{cases} c_l^\varepsilon = \hat{c}_l^\varepsilon, \ (D_l^\varepsilon \nabla c_l^\varepsilon - \mathbf{v}_l^\varepsilon c_l^\varepsilon)\cdot \mathbf{n} = \frac{1}{\varepsilon}(\hat{D}_l^\varepsilon \nabla \hat{c}_l^\varepsilon - \hat{\mathbf{v}}_l^\varepsilon \hat{c}_l^\varepsilon)\cdot \mathbf{n} & \text{on } (\partial\Omega_l^\varepsilon \cap \hat{\Lambda}) \times (0,T), \\ c_s^\varepsilon = \hat{c}_s^\varepsilon, \ D_s^\varepsilon \nabla c_s^\varepsilon \cdot \mathbf{n} = \frac{1}{\varepsilon}\hat{D}_s^\varepsilon \nabla \hat{c}_s^\varepsilon \cdot \mathbf{n} & \text{on } (\partial\Omega_s^\varepsilon \cap \hat{\Lambda}) \times (0,T), \end{cases} \tag{33}$$

where $l = a, v$. We remark that the ε^{-1} scaling in (33) balances the oxygen flux terms in the skin layer with the depth of the layer.

At the external boundaries we consider Dirichlet boundary conditions that define the prescribed oxygen concentration at the arterial/venous blood vessel boundaries and zero-flux boundary conditions at the tissue boundaries:

$$\begin{cases} c_l^\varepsilon = c_{l,D} & \text{on } (\Gamma_D \cap \partial\Omega_l^\varepsilon) \times (0,T), \quad \text{for } l = a, v, \\ D_l^\varepsilon \nabla c_l^\varepsilon \cdot \mathbf{n} = 0 & \text{on } \big((\partial\hat{\Omega} \times (-L,0)) \cap \partial\Omega_l^\varepsilon\big) \times (0,T), \quad \text{for } l = a, v, \\ D_s^\varepsilon \nabla c_s^\varepsilon \cdot \mathbf{n} = 0 & \text{on } \big(\Gamma_D \cup (\partial\hat{\Omega} \times (-L,0)) \cap \partial\Omega_s^\varepsilon\big) \times (0,T), \\ \hat{D}_l^\varepsilon \nabla \hat{c}_l^\varepsilon \cdot \mathbf{n} = 0 & \text{on } ((\hat{\Omega} \times \{\varepsilon\} \cup \partial\hat{\Omega} \times (0,\varepsilon)) \cap \partial\Lambda_l^\varepsilon) \times (0,T), \quad \text{for } l = a, v, s. \end{cases} \tag{34}$$

The initial conditions for the oxygen concentrations are given by

$$c_l^\varepsilon(0,x) = c_l^0(x) \quad \text{in } \Omega_l^\varepsilon, \quad \hat{c}_l^\varepsilon(0,x) = \hat{c}_l^{\varepsilon,0}(x) \quad \text{in } \Lambda_l^\varepsilon, \quad \text{where} \quad l = a, v, s. \tag{35}$$

In the following, we make use of the notation $\Omega_T = \Omega \times (0,T)$, $\Omega_{l,T}^\varepsilon = \Omega_l^\varepsilon \times (0,T)$, $\Gamma_{D,T} = \Gamma_D \times (0,T)$, $\partial\Omega_T = \partial\Omega \times (0,T)$, and $\Lambda_{l,T}^\varepsilon = \Lambda_l^\varepsilon \times (0,T)$ for $l = a, v, s$. We also use the notation $\hat{\Lambda}_T = \hat{\Lambda} \times (0,T)$, $\partial\hat{\Lambda}_T = \partial\hat{\Lambda} \times (0,T)$, and $\hat{Z} = Z \cap \{x_n = 0\}$. The diffusion coefficients D_l^ε, $\hat{D}_l^\varepsilon$ and the oxygen degradation rates d_s^ε, $\hat{d}_s^\varepsilon$ are defined by Y-periodic and $\hat{Z}$-periodic functions D_l, d_s and $\hat{D}_l$, $\hat{d}_s$, respectively. Specifically,

$$D_l^\varepsilon(x) = D_l(x/\varepsilon), \hat{D}_l^\varepsilon(x) = \hat{D}_l(x/\varepsilon), d_s^\varepsilon(t,x) = d_s(t,x/\varepsilon), \text{and } \hat{d}_s^\varepsilon(t,x) = \hat{d}_s(t,x/\varepsilon),$$

for a.a. $t \geq 0$, $x \in \Omega$, $x \in \Lambda^\varepsilon$, and $l = a, v, s$. Finally, the following assumption is made throughout the paper.

Assumption 3.1 The following hold:

(i) The diffusion coefficients $D_l \in L^\infty(Y)$, $\hat{D}_l \in L^\infty(Z)$ are uniformly elliptic, i.e., $(D_l(y)\xi, \xi) \geq D_0|\xi|^2$, $(\hat{D}_l(z)\xi, \xi) \geq \hat{D}_0|\xi|^2$ for all $\xi \in \mathbb{R}^n$ and a.a. $y \in Y$ and $z \in Z$, where $l = a, v, s$, and $D_0 > 0$, $\hat{D}_0 > 0$.

(ii) It is assumed that $d_s, \partial_t d_s \in L^\infty((0,T) \times Y)$ and $\hat{d}_s, \partial_t \hat{d}_s \in L^\infty((0,T) \times Z)$.

(iii) With respect to the initial conditions, it is assumed that $c_l^0 \in H^2(\Omega) \cap L^\infty(\Omega)$, $\hat{c}_l^{\varepsilon,0} \in H^2(\Lambda^\varepsilon) \cap L^\infty(\Lambda^\varepsilon)$, $c_l^0(x) \geq 0$ for $x \in \Omega$, $\hat{c}_l^{\varepsilon,0}(x) \geq 0$ for $x \in \Lambda^\varepsilon$, $l = a, v, s$, $\hat{c}_a^{\varepsilon,0} = \hat{c}_v^{\varepsilon,0} = \hat{c}^{\varepsilon,0}$, and $c_l^0(x) = c_{l,D}(0,x)$ on Γ_D, where $l = a, v$. Moreover,

$$\varepsilon^{-1}\|\hat{c}_l^{\varepsilon,0}\|^2_{H^2(\Lambda^\varepsilon)} \leq C, \qquad \|\hat{c}_l^{\varepsilon,0}\|_{L^\infty(\Lambda^\varepsilon)} \leq C,$$

$$c_l^0(x) = \hat{c}_l^{\varepsilon,0}(x), \quad D_l^\varepsilon(x)\nabla c_l^0(x) \cdot \mathbf{n} = \frac{1}{\varepsilon}\hat{D}_l^\varepsilon(x)\nabla \hat{c}_l^{\varepsilon,0}(x) \cdot \mathbf{n} \ \text{ on } \ \partial\Omega_l^\varepsilon \cap \hat{\Lambda}.$$

(iv) It is assumed that the boundary conditions for the oxygen concentration in arteries and veins satisfy $c_{l,D} \in H^1(0,T;H^2(\Omega)) \cap L^\infty(\Omega_T)$, $\partial_t c_{l,D} \in$

$L^\infty(\Omega_T) \cap H^1(0,T;L^2(\Omega))$, $c_{l,D}(t,x) \geq 0$ a.e. in Ω_T, and $c_{l,D}(t,x) = 0$ on $\hat{\Lambda}_T$, for $l = a, v$.

(v) Finally, it is assumed that $\mu > 0$, $\lambda_l > 0$, $\hat{\lambda}_l > 0$, and $p_l^0 > 0$ for $l = a, v$.

4. Weak solutions and functional spaces

The microscopic system under consideration consists of equations (22)–(27) for the blood velocity fields and pressures in arteries and veins, and equations (28)–(35) for the oxygen concentrations in arteries, veins, and tissue. We now define a notion of weak solution for the system of equations (22)–(35) and the functional spaces that are used in this paper. We start by defining the spaces

$$
\begin{aligned}
V(\Omega_l^\varepsilon) &= \big\{v \in H^1(\Omega_l^\varepsilon), \quad v \times \mathbf{n} = 0 \ \text{ on } \Gamma_D \cap \partial\Omega_l^\varepsilon, \\
&\qquad\qquad\qquad\quad v = 0 \ \text{ on } \Gamma_l^\varepsilon \cup (\partial\hat{\Omega} \times (-L,0) \cap \partial\Omega_l^\varepsilon)\big\}, \\
\hat{V}(\Lambda_l^\varepsilon) &= \{v \in H^1(\Lambda_l^\varepsilon), \quad v = 0 \ \text{ on } R_l^\varepsilon \text{ and } ((\partial\hat{\Omega} \times (0,\varepsilon)) \cup (\hat{\Omega} \times \{\varepsilon\})) \cap \partial\Lambda_l^\varepsilon\}, \\
W(\Omega_l^\varepsilon) &= \{w \in H^1(\Omega_l^\varepsilon), \ \ w = 0 \ \text{ on } \Gamma_D \cap \partial\Omega_l^\varepsilon\}, \\
W(\Omega) &= \{w \in H^1(\Omega), \quad w = 0 \ \text{ on } \Gamma_D\}, \\
V_d(\Omega_l^\varepsilon) &= \{v \in V(\Omega_l^\varepsilon), \ \mathrm{div} v = 0\}, \qquad\quad \hat{V}_d(\Lambda_l^\varepsilon) = \{v \in \hat{V}(\Lambda_l^\varepsilon), \ \mathrm{div} v = 0\},
\end{aligned}
$$

where $l = a, v$. For $\phi, \psi \in L^2((0,\sigma) \times \Omega)$ we make use of the notation

$$
\langle \phi, \psi \rangle_{\Omega,\sigma} = \int_0^\sigma \int_\Omega \phi\psi \, dxdt.
$$

In the remainder of the paper we make use of the auxiliary variable $\tilde{p}_l^\varepsilon$ instead of p_l^ε, where

$$
\tilde{p}_l^\varepsilon(x) \ = \ p_l^\varepsilon(x) + \frac{x_n}{L} p_l^0 \ \text{ in } \ \Omega_l^\varepsilon,
$$

$l = a, v$. The introduction of $\tilde{p}_l^\varepsilon$ allows us to focus on zero Dirichlet boundary conditions for the pressure. Also, for the sake of notational simplicity, in what follows we omit the tilde $\sim$ and write p_l^ε instead of $\tilde{p}_l^\varepsilon$. We remark that the use of $\mathbf{v}_l^\varepsilon \times \mathbf{n} = 0$ on $\Gamma_D \cap \partial\Omega_l^\varepsilon$ and $\mathrm{div}\, \mathbf{v}_l^\varepsilon = 0$ in Ω_l^ε, along with the fact that Γ_D is a flat boundary, lead to $\partial_{x_n} \mathbf{v}_l^\varepsilon \cdot \mathbf{n} = 0$ and, hence, $\langle \mathrm{S}\mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \phi_l \rangle_{\Gamma_D \cap \partial\Omega_l^\varepsilon} = 0$ for $\mathbf{v}_l^\varepsilon \in V_d(\Omega_l^\varepsilon)$ and $\phi_l \in V(\Omega_l^\varepsilon)$, where $l = a, v$.

We are interested in the existence of weak solutions to the system of equations (22)–(35).

Definition 1 A weak solution of the problem (22)–(27) consists of functions $\mathbf{v}_l^\varepsilon \in V_d(\Omega_l^\varepsilon)$, $p_l^\varepsilon \in L^2(\Omega_l^\varepsilon)$, $\hat{\mathbf{v}}_l^\varepsilon \in \hat{V}_d(\Lambda_l^\varepsilon)$, and $\hat{p}_l^\varepsilon \in L^2(\Lambda_l^\varepsilon)$, $l = a, v$, that satisfy the equation

$$
\begin{aligned}
&\sum_{l=a,v} \Big[\langle 2\mu\varepsilon^2 \, \mathrm{S}\mathbf{v}_l^\varepsilon, \mathrm{S}\phi_l \rangle_{\Omega_l^\varepsilon} - \langle p_l^\varepsilon, \mathrm{div}\, \phi_l \rangle_{\Omega_l^\varepsilon} - \frac{1}{L} \langle p_l^0, \phi_{l,n} \rangle_{\Omega_l^\varepsilon} \Big] \\
&+ \frac{1}{\varepsilon} \sum_{l=a,v} \Big[\langle 2\mu\varepsilon^2 \, \mathrm{S}\hat{\mathbf{v}}_l^\varepsilon, \mathrm{S}\hat{\phi}_l \rangle_{\Lambda_l^\varepsilon} - \langle \hat{p}_l^\varepsilon, \mathrm{div}\, \hat{\phi}_l \rangle_{\Lambda_l^\varepsilon} \Big] = 0
\end{aligned}
\tag{36}
$$

for all $\phi_l \in V(\Omega_l^\varepsilon)$ and $\hat{\phi}_l \in \hat{V}(\Lambda_l^\varepsilon)$ with $\phi_l = \frac{1}{\varepsilon}\hat{\phi}_l$ on $\hat{\Lambda} \cap \partial\Omega_l^\varepsilon$ and $\hat{\phi}_a = \hat{\phi}_v$ on Σ^ε.

A weak solution of the problem (28)–(35) consists of functions $c_l^\varepsilon - c_{l,D} \in L^2(0,T;W(\Omega_l^\varepsilon))$, $\partial_t c_l^\varepsilon \in L^2(\Omega_{l,T}^\varepsilon)$, $c_s^\varepsilon \in L^2(0,T;H^1(\Omega_s^\varepsilon))$, $\hat{c}_l^\varepsilon \in L^2(0,T;H^1(\Lambda_l^\varepsilon)) \cap H^1(0,T;L^2(\Lambda_l^\varepsilon))$, $c_l^\varepsilon \in L^\infty(\Omega_{l,T}^\varepsilon)$, and $\hat{c}_l^\varepsilon \in L^\infty(\Lambda_{l,T}^\varepsilon)$, $l = a, v, s$, which satisfy the equations

$$\sum_{l=a,v} \Big[\langle \partial_t c_l^\varepsilon, \psi_l \rangle_{\Omega_l^\varepsilon, T} + \langle D_l^\varepsilon \nabla c_l^\varepsilon - \mathbf{v}_l^\varepsilon c_l^\varepsilon, \nabla \psi_l \rangle_{\Omega_l^\varepsilon, T} - \varepsilon \langle \lambda_l (c_s^\varepsilon - c_l^\varepsilon), \psi_l \rangle_{\Gamma_l^\varepsilon, T} \Big] \tag{37}$$
$$+ \frac{1}{\varepsilon} \sum_{l=a,v} \Big[\langle \partial_t \hat{c}_l^\varepsilon, \hat{\psi}_l \rangle_{\Lambda_l^\varepsilon, T} + \langle \hat{D}_l^\varepsilon \nabla \hat{c}_l^\varepsilon - \hat{\mathbf{v}}_l^\varepsilon \hat{c}_l^\varepsilon, \nabla \hat{\psi}_l \rangle_{\Lambda_l^\varepsilon, T} - \varepsilon \langle \hat{\lambda}_l (\hat{c}_s^\varepsilon - \hat{c}_l^\varepsilon), \hat{\psi}_l \rangle_{R_l^\varepsilon, T} \Big] = 0$$

for all $\psi_l \in L^2(0,T;W(\Omega_l^\varepsilon))$ and $\hat{\psi}_l \in L^2(0,T;H^1(\Lambda_l^\varepsilon))$ with $\psi_l = \hat{\psi}_l$ on $(\hat{\Lambda} \cap \partial\Omega_l^\varepsilon) \times (0,T)$ and $\hat{\psi}_a = \hat{\psi}_v$ on $\Sigma^\varepsilon \times (0,T)$, and

$$\begin{aligned} &\langle \partial_t c_s^\varepsilon, \psi_s \rangle_{\Omega_s^\varepsilon, T} + \langle D_s^\varepsilon \nabla c_s^\varepsilon, \nabla \psi_s \rangle_{\Omega_s^\varepsilon, T} + \langle d_s^\varepsilon c_s^\varepsilon, \psi_s \rangle_{\Omega_s^\varepsilon, T} \\ &+ \frac{1}{\varepsilon} \Big[\langle \partial_t \hat{c}_s^\varepsilon, \hat{\psi}_s \rangle_{\Lambda_s^\varepsilon, T} + \langle \hat{D}_s^\varepsilon \nabla \hat{c}_s^\varepsilon, \nabla \hat{\psi}_s \rangle_{\Lambda_s^\varepsilon, T} + \langle \hat{d}_s^\varepsilon \hat{c}_s^\varepsilon, \hat{\psi}_s \rangle_{\Lambda_s^\varepsilon, T} \Big] \\ &= \varepsilon \sum_{l=a,v} \langle \lambda_l (c_l^\varepsilon - c_s^\varepsilon), \psi_s \rangle_{\Gamma_l^\varepsilon, T} + \sum_{l=a,v} \langle \hat{\lambda}_l (\hat{c}_l^\varepsilon - \hat{c}_s^\varepsilon), \hat{\psi}_s \rangle_{R_l^\varepsilon, T}, \end{aligned} \tag{38}$$

for all $\psi_s \in L^2(0,T;H^1(\Omega_s^\varepsilon))$ and $\hat{\psi}_s \in L^2(0,T;H^1(\Lambda_s^\varepsilon))$ with $\psi_s = \hat{\psi}_s$ on $(\hat{\Lambda} \cap \partial\Omega_s^\varepsilon) \times (0,T)$, and $c_l^\varepsilon \to c_l^0$ in $L^2(\Omega_l^\varepsilon)$, $\hat{c}_l^\varepsilon \to \hat{c}_l^{\varepsilon,0}$ in $L^2(\Lambda_l^\varepsilon)$ as $t \to 0$, for $l = a, v, s$.

Theorem 4.1 *For each $\varepsilon > 0$ there exists a unique weak solution of the microscopic model* (22)–(35).

Sketch of proof. A priori estimates similar to those shown below in Lemma 5.1, along with well-known results on the well-posedness of the Stokes equations and parabolic systems, ensure the existence and uniqueness of a solution to the system (22)–(35). We remark that the Dirichlet boundary conditions for the pressure on the boundary Γ_D, see (24), ensure the uniqueness of the pressure. ■

5. A priori estimates and convergence results

We now turn our attention to deriving *a priori* estimates for the weak solutions of the microscopic model (22)–(35). The *a priori* estimates are then used in conjunction with the notion of two-scale convergence and an unfolding operator approach to establish the convergence of the solutions as $\varepsilon \to 0$.

Lemma 5.1 *Under Assumption 3.1 the solutions of the problem* (22)–(27) *satisfy the a priori estimates*

$$\|\mathbf{v}_l^\varepsilon\|_{L^2(\Omega_l^\varepsilon)} + \varepsilon \|\nabla \mathbf{v}_l^\varepsilon\|_{L^2(\Omega_l^\varepsilon)} + \frac{1}{\sqrt{\varepsilon}} \|\hat{\mathbf{v}}_l^\varepsilon\|_{L^2(\Lambda_l^\varepsilon)} + \sqrt{\varepsilon} \|\nabla \hat{\mathbf{v}}_l^\varepsilon\|_{L^2(\Lambda_l^\varepsilon)} \leq C, \tag{39}$$

where $l = a, v$. Moreover, there exist extensions P_a^ε, P_v^ε and $\hat{P}^\varepsilon$ of p_a^ε, p_v^ε and $\hat{p}^\varepsilon = \hat{p}_a^\varepsilon \chi_{\Lambda_a^\varepsilon} + \hat{p}_v^\varepsilon \chi_{\Lambda_v^\varepsilon}$ respectively, such that

$$\|P_a^\varepsilon\|_{L^2(\Omega)} + \|P_v^\varepsilon\|_{L^2(\Omega)} + \frac{1}{\sqrt{\varepsilon}} \|\hat{P}^\varepsilon\|_{L^2(\Lambda^\varepsilon)} \leq C. \tag{40}$$

Finally, the solutions of the problem (28)–(35)*, i.e. the oxygen concentrations in arteries, veins, and tissue, satisfy the estimates*

$$\begin{aligned}
&\|c_l^\varepsilon\|_{L^\infty(0,T;L^2(\Omega_l^\varepsilon))} + \|\nabla c_l^\varepsilon\|_{L^2((0,T)\times\Omega_l^\varepsilon)} \le C,\\
&\frac{1}{\sqrt{\varepsilon}}\|\hat{c}_l^\varepsilon\|_{L^\infty(0,T;L^2(\Lambda_l^\varepsilon))} + \frac{1}{\sqrt{\varepsilon}}\|\nabla \hat{c}_l^\varepsilon\|_{L^2((0,T)\times\Lambda_l^\varepsilon)} \le C,\\
&c_l^\varepsilon(t,x) \ge 0 \ \text{a.e. in } \Omega_{l,T}^\varepsilon, \quad \hat{c}_l^\varepsilon(t,x) \ge 0 \ \text{a.e. in } \Lambda_{l,T}^\varepsilon,\\
&\|c_l^\varepsilon\|_{L^\infty(\Omega_{l,T}^\varepsilon)} + \|\hat{c}_l^\varepsilon\|_{L^\infty(\Lambda_{l,T}^\varepsilon)} \le C,\\
&\|\partial_t c_l^\varepsilon\|_{L^\infty(0,T;L^2(\Omega_l^\varepsilon))} + \|\partial_t \nabla c_l^\varepsilon\|_{L^2((0,T)\times\Omega_l^\varepsilon))} \le C,\\
&\frac{1}{\sqrt{\varepsilon}}\|\partial_t \hat{c}_l^\varepsilon\|_{L^\infty(0,T;L^2(\Lambda_l^\varepsilon))} + \frac{1}{\sqrt{\varepsilon}}\|\partial_t \nabla \hat{c}_l^\varepsilon\|_{L^2((0,T)\times\Lambda_l^\varepsilon))} \le C,
\end{aligned} \tag{41}$$

where $l = a, v, s$*. Here the constant* C *is independent of* ε*.*

Proof. Using $\mathbf{v}_l^\varepsilon = 0$ on Γ_l^ε and $\big(\partial\hat{\Omega} \times (-L, 0)\big) \cap \partial\Omega_l^\varepsilon$, and $\hat{\mathbf{v}}_l^\varepsilon = 0$ on R_l^ε and $\big(\partial\hat{\Omega} \times (0,\varepsilon) \cup \hat{\Omega} \times \{\varepsilon\}\big) \cap \partial\Lambda_l^\varepsilon$, and applying Poincaré's and Korn's inequalities [2, 4, 17, 34], we obtain

$$\begin{aligned}
&\|\mathbf{v}^\varepsilon\|^2_{L^2(\Omega_l^\varepsilon)} + \varepsilon^2\|\nabla \mathbf{v}^\varepsilon\|^2_{L^2(\Omega_l^\varepsilon)} \le C\varepsilon^2\|\,\mathrm{S}\mathbf{v}^\varepsilon\|^2_{L^2(\Omega_l^\varepsilon)},\\
&\|\hat{\mathbf{v}}^\varepsilon\|^2_{L^2(\Lambda_l^\varepsilon)} + \varepsilon^2\|\nabla \hat{\mathbf{v}}^\varepsilon\|^2_{L^2(\Lambda_l^\varepsilon)} \le C\varepsilon^2\|\,\mathrm{S}\hat{\mathbf{v}}^\varepsilon\|^2_{L^2(\Lambda_l^\varepsilon)},
\end{aligned} \tag{42}$$

with a constant C independent of ε. Considering $\mathbf{v}_l^\varepsilon$ and $\hat{\mathbf{v}}_l^\varepsilon$, where $l = a, v$, as test functions in the weak formulation (36), using the divergence-free property of the blood velocity fields, and applying (42) imply the estimates in (39).

Due to the continuity conditions on Σ^ε we can define $\hat{p}^\varepsilon = \hat{p}_a^\varepsilon \chi_{\Lambda_a^\varepsilon} + \hat{p}_v^\varepsilon \chi_{\Lambda_v^\varepsilon}$. As in [2] we can construct a restriction operator, which is a linear continuous operator $\mathcal{R}_l^\varepsilon : H_0^1(\Omega) \to H_0^1(\Omega_l^\varepsilon)$ such that

(i) $u \in H_0^1(\Omega_l^\varepsilon)$ implies $\mathcal{R}_l^\varepsilon \tilde{u} = u$ in Ω_l^ε, where $\tilde{u}$ is an extension of u by zero in Ω.
(ii) $\operatorname{div} u = 0$ in Ω implies $\operatorname{div}(\mathcal{R}_l^\varepsilon u) = 0$ in Ω_l^ε.
(iii) For each $u \in H_0^1(\Omega)$ the following estimate holds

$$\|\mathcal{R}_l^\varepsilon u\|_{L^2(\Omega_l^\varepsilon)} + \varepsilon\|\nabla \mathcal{R}_l^\varepsilon u\|_{L^2(\Omega_l^\varepsilon)} \le C\left[\|u\|_{L^2(\Omega)} + \varepsilon\|\nabla u\|_{L^2(\Omega)}\right]$$

with the constant C being independent of ε. A similar restriction operator can be defined for $\Lambda^\varepsilon = \hat{\Omega} \times (0, \varepsilon)$ as a linear continuous operator $\hat{\mathcal{R}}^\varepsilon : H_0^1(\Lambda^\varepsilon) \to H_0^1(\Lambda_{av}^\varepsilon)$, where $\Lambda_{av}^\varepsilon = \Lambda_a^\varepsilon \cup \Sigma^\varepsilon \cup \Lambda_v^\varepsilon$. Using the properties of $\mathcal{R}_l^\varepsilon$ and $\hat{\mathcal{R}}^\varepsilon$, where $l = a, v$, we can extend p_l^ε from Ω_l^ε into Ω, and $\hat{p}^\varepsilon$ from Λ_{av}^ε into Λ^ε. These extensions satisfy the *a priori* estimates in (40) (see e.g., [2]). In particular, for the construction of the extension of $\hat{p}^\varepsilon$, we consider a linear functional F^ε in $H^{-1}(\Lambda^\varepsilon)$ defined as

$$\langle F^\varepsilon, \psi\rangle_{H^{-1}, H_0^1(\Lambda^\varepsilon)} = \langle \nabla \hat{p}^\varepsilon, \hat{\mathcal{R}}^\varepsilon \psi\rangle_{H^{-1}, H_0^1(\Lambda_{av}^\varepsilon)} \quad \text{for } \psi \in H_0^1(\Lambda^\varepsilon),$$

Using equation (23), the properties of the restriction operator $\hat{\mathcal{R}}^\varepsilon$ and the estimates in (39) we obtain

$$\begin{aligned}
&\langle F^\varepsilon, \psi\rangle_{H^{-1}, H_0^1(\Lambda^\varepsilon)} = \langle \varepsilon^2 \mu \Delta \hat{\mathbf{v}}_{av}^\varepsilon, \hat{\mathcal{R}}^\varepsilon \psi\rangle_{H^{-1}, H_0^1(\Lambda_{av}^\varepsilon)} = -\langle \varepsilon^2 \mu \nabla \hat{\mathbf{v}}_{av}^\varepsilon, \nabla \hat{\mathcal{R}}^\varepsilon \psi\rangle_{\Lambda_{av}^\varepsilon},\\
&\big|\langle F^\varepsilon, \psi\rangle_{H^{-1}, H_0^1(\Lambda^\varepsilon)}\big| \le C_1\sqrt{\varepsilon}\left[\|\psi\|_{L^2(\Lambda^\varepsilon)} + \varepsilon\|\nabla\psi\|_{L^2(\Lambda^\varepsilon)}\right] \le C_2\varepsilon\sqrt{\varepsilon}\|\nabla\psi\|_{L^2(\Lambda^\varepsilon)},
\end{aligned}$$

where $\hat{\mathbf{v}}^\varepsilon_{av} = \hat{\mathbf{v}}^\varepsilon_a \chi_{\Lambda^\varepsilon_a} + \hat{\mathbf{v}}^\varepsilon_v \chi_{\Lambda^\varepsilon_v}$. Thus

$$\frac{1}{\sqrt{\varepsilon}} \|F^\varepsilon\|_{H^{-1}(\Lambda^\varepsilon)} \leq C\varepsilon.$$

Additionally, we have $\langle F^\varepsilon, \psi \rangle_{H^{-1}, H^1_0(\Lambda^\varepsilon)} = 0$ for all $\psi \in H^1_0(\Lambda^\varepsilon)$ with $\operatorname{div} \psi = 0$ in Λ^ε. Hence, there exists $\hat{P}^\varepsilon \in L^2(\Lambda^\varepsilon)/\mathbb{R}$ such that $F^\varepsilon = \nabla \hat{P}^\varepsilon$ and, using the Nečas inequality [22],

$$\frac{1}{\sqrt{\varepsilon}} \|\hat{P}^\varepsilon\|_{L^2(\Lambda^\varepsilon)/\mathbb{R}} \leq \frac{1}{\sqrt{\varepsilon}} \frac{C_1}{\varepsilon} \|F^\varepsilon\|_{H^{-1}(\Lambda^\varepsilon)} \leq C_2.$$

In the same way as in [2] we obtain that $\hat{P}^\varepsilon$ is an extension of $\hat{p}^\varepsilon$. The fact that $\hat{p}^\varepsilon$ is uniquely defined implies that $\hat{P}^\varepsilon \in L^2(\Lambda^\varepsilon)$.

Using that $c^\varepsilon_l - c_{l,D} = 0$ on $\Gamma_D \cap \partial\Omega^\varepsilon_l$ and $c_{l,D} = 0$ on $\hat{\Lambda}$, in conjunction with (a) the divergence-free property of $\mathbf{v}^\varepsilon_l$ and $\hat{\mathbf{v}}^\varepsilon_l$, (b) the zero-boundary conditions for $\mathbf{v}^\varepsilon_l$ and $\hat{\mathbf{v}}^\varepsilon_l$, and (c) the continuity of concentrations on $\hat{\Lambda} \cap \partial\Lambda^\varepsilon_l$, we obtain

$$\begin{aligned} \langle \mathbf{v}^\varepsilon_l c^\varepsilon_l, \nabla(c^\varepsilon_l - c_{l,D}) \rangle_{\Omega^\varepsilon_l} + \frac{1}{\varepsilon} \langle \hat{\mathbf{v}}^\varepsilon_l \hat{c}^\varepsilon_l, \nabla \hat{c}^\varepsilon_l \rangle_{\Lambda^\varepsilon_l} = \langle \mathbf{v}^\varepsilon_l c_{l,D}, \nabla(c^\varepsilon_l - c_{l,D}) \rangle_{\Omega^\varepsilon_l} \\ + \frac{1}{2} \langle \mathbf{v}^\varepsilon_l \cdot \mathbf{n}, |c^\varepsilon_l|^2 \rangle_{\hat{\Lambda} \cap \partial\Lambda^\varepsilon_l} - \frac{1}{2\varepsilon} \langle \hat{\mathbf{v}}^\varepsilon_l \cdot \mathbf{n}, |\hat{c}^\varepsilon_l|^2 \rangle_{\hat{\Lambda} \cap \partial\Lambda^\varepsilon_l} \leq \frac{1}{2\sigma} \|\mathbf{v}^\varepsilon_l\|^2_{L^2(\Omega^\varepsilon_l)} \|c_{l,D}\|^2_{L^\infty(\Omega^\varepsilon_l)} \\ + \frac{\sigma}{2} \left(\|\nabla c^\varepsilon_l\|^2_{L^2(\Omega^\varepsilon_l)} + \|\nabla c_{l,D}\|^2_{L^2(\Omega^\varepsilon_l)} \right) \end{aligned} \tag{43}$$

for some $\sigma > 0$. Applying the trace inequality [17, 21] we obtain

$$\begin{aligned} \varepsilon \|w\|^2_{L^2(\Gamma^\varepsilon_l)} \leq C \left[\|w\|^2_{L^2(\Omega^\varepsilon_l)} + \varepsilon^2 \|\nabla w\|^2_{L^2(\Omega^\varepsilon_l)} \right], \\ \varepsilon \|w\|^2_{L^2(R^\varepsilon_l)} \leq C \left[\|w\|^2_{L^2(\Lambda^\varepsilon_l)} + \varepsilon^2 \|\nabla w\|^2_{L^2(\Lambda^\varepsilon_l)} \right], \end{aligned} \tag{44}$$

where $l = a, v, s$, C is independent of ε, $\Gamma_s = \Gamma_a \cup \Gamma_v$, and $R_s = R_a \cup R_v$. Now considering $c^\varepsilon_l - c_{l,D}$ and $\hat{c}^\varepsilon_l$ as test functions in (37)–(38) and applying estimates (43) and (44) we obtain the first estimates in (41).

In order to show the non-negativity of c^ε_l and $\hat{c}^\varepsilon_l$, we consider $c^{\varepsilon,-}_l = \min\{c^\varepsilon_l, 0\}$ and $\hat{c}^{\varepsilon,-}_l = \min\{\hat{c}^\varepsilon_l, 0\}$ as test functions to derive:

$$\begin{aligned} &\sum_{l=a,v} \left[\partial_t \|c^{\varepsilon,-}_l\|^2_{L^2(\Omega^\varepsilon_l)} + \|\nabla c^{\varepsilon,-}_l\|^2_{L^2(\Omega^\varepsilon_l)} + \varepsilon \|c^{\varepsilon,-}_l\|^2_{L^2(\Gamma^\varepsilon_l)} - \langle \mathbf{v}^\varepsilon_l c^{\varepsilon,-}_l, \nabla c^{\varepsilon,-}_l \rangle_{\Omega^\varepsilon_l} \right] \\ &+ \sum_{l=a,v} \left[\frac{1}{\varepsilon} \partial_t \|\hat{c}^{\varepsilon,-}_l\|^2_{L^2(\Lambda^\varepsilon_l)} + \frac{1}{\varepsilon} \|\nabla \hat{c}^{\varepsilon,-}_l\|^2_{L^2(\Lambda^\varepsilon_l)} + \|\hat{c}^{\varepsilon,-}_l\|^2_{L^2(R^\varepsilon_l)} - \frac{1}{\varepsilon} \langle \hat{\mathbf{v}}^\varepsilon_l \hat{c}^{\varepsilon,-}_l, \nabla \hat{c}^{\varepsilon,-}_l \rangle_{\Lambda^\varepsilon_l} \right] \\ &- \sum_{l=a,v} \left[\hat{\lambda}_l \langle \hat{c}^{\varepsilon,+}_s, \hat{c}^{\varepsilon,-}_l \rangle_{R^\varepsilon_l} + \varepsilon \lambda_l \langle c^{\varepsilon,+}_s, c^{\varepsilon,-}_l \rangle_{\Gamma^\varepsilon_l} \right] \leq C \sum_{l=a,v} \left[\varepsilon \langle c^{\varepsilon,-}_s, c^{\varepsilon,-}_l \rangle_{\Gamma^\varepsilon_l} + \langle \hat{c}^{\varepsilon,-}_s, \hat{c}^{\varepsilon,-}_l \rangle_{R^\varepsilon_l} \right]. \end{aligned}$$

Similarly, for the oxygen concentration in the surrounding tissue, we have

$$
\begin{aligned}
&\partial_t \|c_s^{\varepsilon,-}\|^2_{L^2(\Omega_s^\varepsilon)} + \|\nabla c_s^{\varepsilon,-}\|^2_{L^2(\Omega_s^\varepsilon)} + \frac{1}{\varepsilon}\partial_t \|\hat{c}_s^{\varepsilon,-}\|^2_{L^2(\Lambda_s^\varepsilon)} + \frac{1}{\varepsilon}\|\nabla \hat{c}_s^{\varepsilon,-}\|^2_{L^2(\Lambda_s^\varepsilon)} \\
&\sum_{l=a,v}\Big[\varepsilon \|c_s^{\varepsilon,-}\|^2_{L^2(\Gamma_l^\varepsilon)} + \|\hat{c}_s^{\varepsilon,-}\|^2_{L^2(R_l^\varepsilon)} - \varepsilon\lambda_l \langle c_s^{\varepsilon,-}, c_l^{\varepsilon,+}\rangle_{\Gamma_l^\varepsilon} - \hat{\lambda}_l \langle \hat{c}_s^{\varepsilon,-}, \hat{c}_l^{\varepsilon,+}\rangle_{R_l^\varepsilon}\Big] \\
&\qquad\qquad \leq C\sum_{l=a,v}\Big[\varepsilon \langle c_s^{\varepsilon,-}, c_l^{\varepsilon,-}\rangle_{\Gamma_l^\varepsilon} + \langle \hat{c}_s^{\varepsilon,-}, \hat{c}_l^{\varepsilon,-}\rangle_{R_l^\varepsilon}\Big],
\end{aligned}
$$

where $c_l^{\varepsilon,+} = \max\{0, c_l^\varepsilon\}$ and $\hat{c}_l^{\varepsilon,+} = \max\{0, \hat{c}_l^\varepsilon\}$. Using the boundary conditions for $\mathbf{v}_l^\varepsilon$, $\hat{\mathbf{v}}_l^\varepsilon$, c_l^ε and $\hat{c}_l^\varepsilon$, we obtain that

$$
-\langle \mathbf{v}_l^\varepsilon c_l^{\varepsilon,-}, \nabla c_l^{\varepsilon,-}\rangle_{\Omega_l^\varepsilon} - \frac{1}{\varepsilon}\langle \hat{\mathbf{v}}_l^\varepsilon \hat{c}_l^{\varepsilon,-}, \nabla \hat{c}_l^{\varepsilon,-}\rangle_{\Lambda_l^\varepsilon} = 0
$$

for $l = a, v$. Combining the last two inequalities and applying estimates (44) and the Gronwall inequality, we obtain that $c_l^{\varepsilon,-}(t,x) = 0$ a.e. in $\Omega_{l,T}^\varepsilon$ and $\hat{c}_l^{\varepsilon,-}(t,x) = 0$ a.e. in $\Lambda_{l,T}^\varepsilon$ for $l = a, v, s$.

To show the boundedness of c_l^ε and $\hat{c}_l^\varepsilon$ we consider $(c_l^\varepsilon - A)^+$ and $(\hat{c}_l^\varepsilon - A)^+$ as test functions in (37)–(38), where $A \geq \max\limits_{l=a,v,s}\{\sup_{\Omega_T} c_{l,D}(t,x), \sup_\Omega c_l^0(x), \sup_{\Lambda^\varepsilon} \hat{c}_l^{\varepsilon,0}(x)\}$. Then, due to the prescribed boundary conditions, we have

$$
-\langle \mathbf{v}_l^\varepsilon c_l^\varepsilon, \nabla (c_l^\varepsilon - A)^+\rangle_{\Omega_l^\varepsilon} - \frac{1}{\varepsilon}\langle \hat{\mathbf{v}}_l^\varepsilon \hat{c}_l^\varepsilon, \nabla (\hat{c}_l^\varepsilon - A)^+\rangle_{\Lambda_l^\varepsilon} = 0
$$

for $l = a, v$, and thus

$$
\begin{aligned}
&\sum_{l=a,v,s}\Big[\partial_t \|(c_l^\varepsilon - A)^+\|^2_{L^2(\Omega_l^\varepsilon)} + \|\nabla (c_l^\varepsilon - A)^+\|^2_{L^2(\Omega_l^\varepsilon)} + \varepsilon \|(c_l^\varepsilon - A)^+\|^2_{L^2(\Gamma_l^\varepsilon)} \\
&\quad \frac{1}{\varepsilon}\partial_t \|(\hat{c}_l^\varepsilon - A)^+\|^2_{L^2(\Lambda_l^\varepsilon)} + \frac{1}{\varepsilon}\|\nabla (\hat{c}_l^\varepsilon - A)^+\|^2_{L^2(\Lambda_l^\varepsilon)} + \|(\hat{c}_l^\varepsilon - A)^+\|^2_{L^2(R_l^\varepsilon)}\Big] \\
&\quad\leq C\sum_{l=a,v}\Big[\varepsilon \langle (c_s^\varepsilon - A)^+, (c_l^\varepsilon - A)^+\rangle_{\Gamma_l^\varepsilon} + \langle (\hat{c}_s^\varepsilon - A)^+, (\hat{c}_l^\varepsilon - A)^+\rangle_{R_l^\varepsilon}\Big].
\end{aligned}
$$

Thus, applying estimates (44) together with the Gronwall inequality, we conclude that $(c_l^\varepsilon(t,x) - A)^+ = 0$ a.e. in $\Omega_{l,T}^\varepsilon$ and $(\hat{c}_l^\varepsilon(t,x) - A)^+ = 0$ a.e. in $\Lambda_{l,T}^\varepsilon$ with $l = a, v, s$. Therefore, the second part of the estimates in (41) follows.

Finally, differentiating equations (28) and (29) with respect to time, and using (a) $\partial_t(c_l^\varepsilon - c_{l,D})$ and $\partial_t \hat{c}_l^\varepsilon$, respectively, as test functions, and (b) the regularity assumptions on the initial values c_l^0 and $\hat{c}_l^{\varepsilon,0}$, yield the estimates for the time derivatives in (41). ■

To derive the macroscopic equations we employ the notion of two-scale convergence [3, 27] and the unfolding method [8, 9]. We denote by $\mathcal{T}_\varepsilon^* : L^p(\Omega_l^\varepsilon) \to L^p(\Omega \times Y_l)$ the unfolding operator and by $\mathcal{T}_\varepsilon^b : L^p(\Gamma_l^\varepsilon) \to L^p(\Omega \times \Gamma_l)$ the boundary unfolding operator, for $p \in [1, \infty)$ (see, e.g., [8, 9]). As in [10, 26] we also define unfolding operators in the thin layer Λ_l^ε and on R_l^ε, where $l = a, v, s$, as follows.

Definition 2 For a measurable function ϕ on Λ^ε we define the unfolding operator

$\mathcal{T}_\varepsilon^{bl}$ as

$$\mathcal{T}_\varepsilon^{bl}(\phi)(x,y) = \phi(\varepsilon[(\hat{x},0)/\varepsilon] + \varepsilon y) \quad \text{ for } \hat{x} \in \hat{\Lambda}, \ y \in Z \ .$$

For a measurable function ϕ on Λ_l^ε we define the unfolding operator $\mathcal{T}_\varepsilon^{*,bl}$ as

$$\mathcal{T}_\varepsilon^{*,bl}(\phi)(x,y) = \phi(\varepsilon[(\hat{x},0)/\varepsilon] + \varepsilon y) \quad \text{ for } \hat{x} \in \hat{\Lambda}, \ y \in Z_l \ .$$

For a measurable function ϕ on R_l^ε we define the boundary unfolding operator $\mathcal{T}_\varepsilon^{b,bl}$ as

$$\mathcal{T}_\varepsilon^{b,bl}(\phi)(x,y) = \phi(\varepsilon[(\hat{x},0)/\varepsilon] + \varepsilon y) \quad \text{ for } \hat{x} \in \hat{\Lambda}, \ y \in R_l \ .$$

The definition of the unfolding operator implies directly (see e.g., [10, 26]) that

$$\|\mathcal{T}_\varepsilon^{*,bl}\phi\|^p_{L^p(\hat{\Lambda}\times Z_l)} \leq \varepsilon^{-1}|\hat{Z}|\|\phi\|^p_{L^p(\Lambda_l^\varepsilon)} \quad \text{and} \quad \varepsilon\mathcal{T}_\varepsilon^{*,bl}(\nabla\phi) = \nabla_y \mathcal{T}_\varepsilon^{*,bl}(\phi) \quad \text{ in } \hat{\Lambda}\times Z_l.$$

Theorems 5.2 and 5.3 below are proven in the same manner as the corresponding results in [8, 9]. For the convenience of the reader, we provide short sketches of the proofs.

Theorem 5.2 *Let $\{w^\varepsilon\} \subset W^{1,p}(\Lambda^\varepsilon)$, where $p \in (1,\infty)$ and $\frac{1}{\varepsilon}\|w^\varepsilon\|^p_{W^{1,p}(\Lambda^\varepsilon)} \leq C$. Then, there exist a subsequence (denoted again by w^ε) and functions $w \in W^{1,p}(\hat{\Lambda})$ and $w_1 \in L^p(\hat{\Lambda}; W^{1,p}(Z))$ such that w_1 is $\hat{Z}$–periodic and*

$$\begin{aligned}
\mathcal{T}_\varepsilon^{bl}(w^\varepsilon) &\rightharpoonup w && \text{weakly in } L^p(\hat{\Lambda}; W^{1,p}(Z)),\\
\mathcal{T}_\varepsilon^{bl}(\nabla w^\varepsilon) &\rightharpoonup \nabla_{\hat{x}} w + \nabla_y w_1 && \text{weakly in } L^p(\hat{\Lambda}\times Z) \ .
\end{aligned}$$

Sketch of proof. By rescaling $\tilde{w}^\varepsilon(\hat{x},y) = w^\varepsilon(\hat{x},\varepsilon y)$ and using the assumptions on $\{w^\varepsilon\}$ we obtain that there exists a function $w \in W^{1,p}(\hat{\Lambda})$ with $\tilde{w}^\varepsilon \to w$ in $L^p(\Lambda^1)$ and $\nabla_{\hat{x}}\tilde{w}^\varepsilon \rightharpoonup \nabla_{\hat{x}} w$ in $L^p(\Lambda^1)$. Also, the assumptions on $\{w^\varepsilon\}$ ensure that $\mathcal{T}_\varepsilon^{bl}(w^\varepsilon)$, $\mathcal{T}_\varepsilon^{bl}(\nabla w^\varepsilon)$, and $\nabla_y\mathcal{T}_\varepsilon^{bl}(w^\varepsilon)$ are bounded in $L^p(\hat{\Lambda}\times Z)$. Hence, $\mathcal{T}_\varepsilon^{bl}(w^\varepsilon) \rightharpoonup w$ in $L^p(\hat{\Lambda}; W^{1,p}(Z))$. We now define

$$V^\varepsilon = \frac{1}{\varepsilon}(\mathcal{T}_\varepsilon^{bl}(w^\varepsilon) - \mathcal{M}_\varepsilon^{bl}(w^\varepsilon)), \quad \text{ where } \quad \mathcal{M}_\varepsilon^{bl}(w^\varepsilon) = \frac{1}{|Z|}\int_Z \mathcal{T}_\varepsilon^{bl}(w^\varepsilon)(\,\cdot\,,y)dy.$$

Using the assumptions on w^ε and applying Poincaré's inequality, we have that

$$\begin{aligned}
&\|\nabla_y V^\varepsilon\|_{L^p(\hat{\Lambda}\times Z)} = \|\mathcal{T}_\varepsilon^{bl}(\nabla w^\varepsilon)\|_{L^p(\hat{\Lambda}\times Z)} \leq C_1,\\
&\|V^\varepsilon - \hat{y}^c\cdot\nabla_{\hat{x}} w\|_{L^p(\hat{\Lambda}\times Z)} \leq C_2\|\nabla_y V^\varepsilon - \nabla_{\hat{x}} w\|_{L^p(\hat{\Lambda}\times Z)} \leq C_3,
\end{aligned}$$

where $\hat{y}^c = (y_1 - a_1/2, \dots, y_{n-1} - a_{n-1}/2)$. Then, there exists a function $w_1 \in L^p(\hat{\Lambda}; W^{1,p}(Z))$ such that, up to a subsequence,

$$V^\varepsilon - \hat{y}^c\cdot\nabla_{\hat{x}} w \rightharpoonup w_1 \quad \text{ in } \quad L^p(\hat{\Lambda}; W^{1,p}(Z)).$$

Hence, we have the second convergence result stated in the theorem.

The proof of $\hat{Z}$-periodicity of w_1 follows the same lines as in the case of $\mathcal{T}_\varepsilon$, see e.g. [9]. Specifically, one considers the differences $V^\varepsilon(\hat{x}, y_j^1) - V^\varepsilon(\hat{x}, y_j^0)$ and $\hat{y}_j^{c,1} \cdot \nabla_{\hat{x}} w - \hat{y}_j^{c,0} \cdot \nabla_{\hat{x}} w$, and shows that $w_1(\hat{x}, y_j^1) = w_1(\hat{x}, y_j^0)$ in the weak sense for $j = 1, \dots, n-1$, where $y_j^1 = (y_1, \dots, y_{j-1}, a_j, y_{j+1}, \dots, y_n)$, $y_j^0 = (y_1, \dots, y_{j-1}, 0, y_{j+1}, \dots, y_n)$, and $\hat{Z} = (0, a_1) \times \ldots \times (0, a_{n-1})$. ■

Theorem 5.3 *Let $\{w^\varepsilon\} \subset W^{1,p}(\Lambda_l^\varepsilon)$, where $p \in (1, \infty)$ and $l = a, v, s$, with*

$$\varepsilon^{-1} \|w^\varepsilon\|^p_{L^p(\Lambda_l^\varepsilon)} \leq C, \qquad \varepsilon^{p-1} \|\nabla w^\varepsilon\|^p_{L^p(\Lambda_l^\varepsilon)} \leq C.$$

Then, there exist a subsequence (denoted again by w^ε) and a $\hat{Z}$-periodic function $\hat{w} \in L^p(\hat{\Lambda}; W^{1,p}(Z_l))$, such that

$$\begin{aligned} \mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon) &\rightharpoonup \hat{w} && \text{weakly in } L^p(\hat{\Lambda}; W^{1,p}(Z_l)), \\ \varepsilon \mathcal{T}_\varepsilon^{*,bl}(\nabla w^\varepsilon) &\rightharpoonup \nabla_y \hat{w} && \text{weakly in } L^p(\hat{\Lambda} \times Z_l)\,. \end{aligned}$$

Proof. Due to the assumptions on $\{w^\varepsilon\}$, we obtain that $\mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon)$ is bounded in $L^p(\hat{\Lambda}; W^{1,p}(Z_l))$. Thus, there exists a function $\hat{w}$ such that the stated convergences are satisfied. The $\hat{Z}$-periodicity follows by the fact that for $\psi \in C_0(\hat{\Lambda} \times Z)$,

$$\begin{aligned} &\int_{\hat{\Lambda} \times Z_l} \left[\mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon)(\hat{x}, y + (\hat{e}_j, 0)) - \mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon)(\hat{x}, y) \right] \psi(\hat{x}, y) d\hat{x} dy \\ &= \int_{\hat{\Lambda} \times Z_l} \mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon)(\hat{x}, y)(\psi(\hat{x} - \varepsilon \hat{e}_j, y) - \psi(\hat{x}, y)) d\hat{x} dy \to 0 \quad \text{ as } \varepsilon \to 0, \end{aligned}$$

where $\hat{e}_j$ are standard basis vectors for $j = 1, \dots, n-1$. ■

To prove convergence results for the unfolding operator in the perforated thin layer Λ_l^ε, with $l = a, v, s$, we define an interpolation operator $\mathcal{Q}_\varepsilon^{*,bl}$. First, we introduce the notation:

$$\mathcal{Y} = \mathrm{Int} \bigcup_{k \in \{0,1\}^{d-1}} (\overline{Z} + (k, 0)),\ \hat{\Lambda}_{\mathcal{Y}}^\varepsilon = \mathrm{Int} \bigcup_{\xi \in \Xi_{\mathcal{Y}}^\varepsilon} \varepsilon(\overline{\hat{Z}} + \xi),\ \Lambda_{\mathcal{Y},l}^\varepsilon = \mathrm{Int} \bigcup_{\xi \in \Xi_{\mathcal{Y}}^\varepsilon} \varepsilon(\overline{Z}_l + (\xi, 0)),$$

$$\Xi_{\mathcal{Y}}^\varepsilon = \{\xi \in \mathbb{Z}^{n-1} : \varepsilon(\mathcal{Y} + (\xi, 0)) \subset \Lambda^\varepsilon\},\ \ \hat{\Xi}^\varepsilon = \{\xi \in \mathbb{Z}^{n-1} : \varepsilon(Z + (\xi, 0)) \subset \Lambda^\varepsilon\}.$$

Then, the definition of $\mathcal{Q}_\varepsilon^{*,bl}$ is similar to the one for perforated domains in [8].

Definition 3 The operator $\mathcal{Q}_\varepsilon^{*,bl} : L^p(\Lambda_{l,T}^\varepsilon) \to L^p(0, T; W^{1,\infty}(\hat{\Lambda}_{\mathcal{Y}}^\varepsilon \times (0, \varepsilon)))$ for $p \in [1, +\infty]$ is defined by

$$\mathcal{Q}_\varepsilon^{*,bl}(\phi)(t, \varepsilon\xi) = \frac{1}{|Z_l|} \int_{Z_l} \phi(t, \varepsilon(\xi, 0) + \varepsilon y) dy \quad \text{ for } \xi \in \hat{\Xi}^\varepsilon, \text{ a.a. } t \in (0, T).$$

For $x \in \hat{\Lambda}_{\mathcal{Y}}^\varepsilon \times (0, \varepsilon)$, $\mathcal{Q}_\varepsilon^{*,bl}(\phi)(t, x)$ is defined as the Q_1- interpolant of $\mathcal{Q}_\varepsilon^{*,bl}(\phi)(t, \varepsilon\xi)$ at the vertices of the cell $\varepsilon([\hat{x}/\varepsilon] + \hat{Z})$ with respect to $x_1, \dots, x_{n-1}$ and constant in x_n, for a.a. $t \in (0, T)$.

We remark that $\partial_t \mathcal{Q}_\varepsilon^{*,bl}(\phi) = \mathcal{Q}_\varepsilon^{*,bl}(\partial_t \phi)$ and $\partial_t \mathcal{R}_\varepsilon^{*,bl}(\phi) = \partial_t(\phi - \mathcal{Q}_\varepsilon^{*,bl}(\phi)) =$

$\mathcal{R}_\varepsilon^{*,bl}(\partial_t\phi)$. Lemma 5.4 and Theorem 5.5 below are proven in a similar manner as the corresponding results in [8].

LEMMA 5.4 *For all $\phi \in W^{1,p}(\Lambda_{l,T}^\varepsilon)$, where $p \in (1,+\infty)$, the following estimates hold*

$$\begin{aligned}
\|\mathcal{Q}_\varepsilon^{*,bl}(\phi)\|_{L^p((0,T)\times\hat{\Lambda}_{\mathcal{Y}}^\varepsilon\times(0,\varepsilon))} &\leq C\|\phi\|_{L^p(\Lambda_{l,T}^\varepsilon)}, \\
\|\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(\phi)\|_{L^p((0,T)\times\hat{\Lambda}_{\mathcal{Y}}^\varepsilon\times(0,\varepsilon))} &\leq C\|\nabla\phi\|_{L^p(\Lambda_{l,T}^\varepsilon)}, \\
\|\mathcal{R}_\varepsilon^{*,bl}(\phi)\|_{L^p((0,T)\times\Lambda_{\mathcal{Y},l}^\varepsilon)} &\leq C\varepsilon\|\nabla\phi\|_{L^p(\Lambda_{l,T}^\varepsilon)}, \\
\|\nabla\mathcal{R}_\varepsilon^{*,bl}(\phi)\|_{L^p((0,T)\times\Lambda_{\mathcal{Y},l}^\varepsilon)} &\leq C\|\nabla\phi\|_{L^p(\Lambda_{l,T}^\varepsilon)}, \\
\|\partial_t\mathcal{Q}_\varepsilon^{*,bl}(\phi)\|_{L^p((0,T)\times\hat{\Lambda}_{\mathcal{Y}}^\varepsilon\times(0,\varepsilon))} &\leq C\|\partial_t\phi\|_{L^p(\Lambda_{l,T}^\varepsilon)}, \\
\|\partial_t\mathcal{R}_\varepsilon^{*,bl}(\phi)\|_{L^p((0,T)\times\Lambda_{\mathcal{Y},l}^\varepsilon)} &\leq C\varepsilon\|\partial_t\phi\|_{L^p(\Lambda_{l,T}^\varepsilon)},
\end{aligned}$$

where the constant C is independent of ε.

THEOREM 5.5 *Assume that the sequence $\{w^\varepsilon\} \subset L^p(0,T;W^{1,p}(\Lambda_l^\varepsilon)) \cap W^{1,p}(0,T;L^p(\Lambda_l^\varepsilon))$, with $p \in (1,+\infty)$, satisfies $\varepsilon^{-1}\|w^\varepsilon\|^p_{L^p(0,T;W^{1,p}(\Lambda_l^\varepsilon))} + \varepsilon^{-1}\|\partial_t w^\varepsilon\|^p_{L^p((0,T)\times\Lambda_l^\varepsilon)} \leq C$. Then, there exists a function $w \in L^p(0,T;W^{1,p}(\hat{\Lambda}))$ such that*

$$\begin{aligned}
&\mathcal{T}_\varepsilon^{bl}(\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim) \rightharpoonup w && \textit{weakly in } L^p(\hat{\Lambda}_T;W^{1,p}(Z)), \\
&\mathcal{T}_\varepsilon^{bl}(\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim) \to w && \textit{strongly in } L^p(0,T;L^p_{loc}(\hat{\Lambda};W^{1,p}(Z))), \\
&\mathcal{T}_\varepsilon^{bl}(\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim) \rightharpoonup \nabla_{\hat{x}}w && \textit{weakly in } L^p(\hat{\Lambda}_T\times Z),
\end{aligned} \tag{45}$$

where $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim$ is the extension by zero of $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)$ from $(0,T)\times\hat{\Lambda}_{\mathcal{Y}}^\varepsilon\times(0,\varepsilon)$ into Λ_T^ε.

Sketch of proof. The assumptions on w^ε, the estimates in Lemma 5.4, and the definition of $\mathcal{Q}_\varepsilon^{*,bl}$ ensure the boundedness of $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim$, its time derivative, and $\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim$ in $L^p(\hat{\Lambda}_T)$. Hence, there exists a function $w \in L^p(0,T;W^{1,p}(\hat{\Lambda}))$ such that $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim \to w$ weakly in $L^p(\hat{\Lambda}_T)$ and strongly in $L^p(0,T;L^p_{\text{loc}}(\hat{\Lambda}))$, and $\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim \rightharpoonup \nabla_{\hat{x}}w$ weakly in $L^p(\hat{\Lambda}_T)$. Then, by the properties of $\mathcal{T}_\varepsilon^{bl}$ (see e.g., [10, 26]), and using the fact that $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)$ is constant in x_n, we obtain the first two convergence results in (45).

Lemma 5.4 and the definition of $\mathcal{Q}_\varepsilon^{*,bl}$ ensure the boundedness of $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)|_{\hat{K}\times(0,\varepsilon)}$ in $L^p(0,T;W^{1,p}(\hat{K}\times(0,\varepsilon)))$, where $\hat{K}\subset\hat{\Lambda}$ is a relatively compact open set and $\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)|_{\hat{K}\times(0,\varepsilon)}$ is constant with respect to x_n. Then, using Theorem 5.2, we obtain the existence of a function $w_{1,\hat{K}} \in L^p(\hat{K}_T;W^{1,p}(Z))$, which is constant in y_n and $\hat{Z}$-periodic, such that

$$\mathcal{T}_\varepsilon^{bl}(\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)|_{\hat{K}}) \rightharpoonup \nabla_{\hat{x}}w + \nabla_{\hat{y}}w_{1,\hat{K}} \quad \text{weakly in } L^p(\hat{K}_T\times Z).$$

Due to the fact that $w_{1,K}$ is a polynomial of degree less or equal to one in each y_j, $j=1,\dots,n-1$, and it is constant with respect to y_n and $\hat{Z}$-periodic, it follows that $w_{1,K}$ is constant in y. Then, since $\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim$ is bounded in $L^p(\Lambda^\varepsilon\times(0,T))$, and hence $\mathcal{T}_\varepsilon^{bl}(\nabla_{\hat{x}}\mathcal{Q}_\varepsilon^{*,bl}(w^\varepsilon)^\sim)$ is bounded in $L^p(\hat{\Lambda}_T \times Z)$, we obtain the last convergence in (45). ■

The estimates for $\mathcal{R}_\varepsilon^{*,bl}(w^\varepsilon)$ along with the convergence of $\mathcal{T}_\varepsilon^{*,bl}(\varepsilon^{-1}\mathcal{R}_\varepsilon^{*,bl}(w^\varepsilon))$, given by Theorem 5.3, (and by using Theorem 5.5) imply the following result.

Theorem 5.6 *Let $\{w^\varepsilon\} \subset L^p(0,T;W^{1,p}(\Lambda_l^\varepsilon)) \cap W^{1,p}(0,T;L^p(\Lambda_l^\varepsilon))$, $p \in (1,+\infty)$, with $\frac{1}{\varepsilon}\|w^\varepsilon\|^p_{L^p(0,T;W^{1,p}(\Lambda_l^\varepsilon))} + \frac{1}{\varepsilon}\|\partial_t w^\varepsilon\|^p_{L^p((0,T)\times\Lambda_l^\varepsilon)} \le C$. Then there exist a subsequence (denoted again by $\{w^\varepsilon\}$) and functions $w \in L^p(0,T;W^{1,p}(\hat{\Lambda}))$ and $w_1 \in L^p(\hat{\Lambda}_T;W^{1,p}(Z_l))$ such that w_1 is $\hat{Z}-$periodic and*

$$
\begin{aligned}
\mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon) &\rightharpoonup w && \text{weakly in } L^p(\hat{\Lambda}_T;W^{1,p}(Z_l)),\\
\mathcal{T}_\varepsilon^{*,bl}(w^\varepsilon) &\to w && \text{strongly in } L^p(0,T;L^p_{loc}(\hat{\Lambda};W^{1,p}(Z_l))),\\
\mathcal{T}_\varepsilon^{*,bl}(\nabla w^\varepsilon) &\rightharpoonup \nabla_{\hat{x}} w + \nabla_y w_1 && \text{weakly in } L^p(\hat{\Lambda}_T \times Z_l)\,.
\end{aligned}
$$

Finally, using the notion of two-scale convergence and the properties of the unfolding operator, we can prove the following lemma.

Lemma 5.7 *The following hold.*

1. *There exist subsequences of $\{\mathbf{v}_l^\varepsilon\}$, $\{p_l^\varepsilon\}$, $\{\hat{\mathbf{v}}_l^\varepsilon\}$, and $\{\hat{p}_l^\varepsilon\}$ (denoted again by $\{\mathbf{v}_l^\varepsilon\}$, $\{p_l^\varepsilon\}$, $\{\hat{\mathbf{v}}_l^\varepsilon\}$, and $\{\hat{p}_l^\varepsilon\}$) and functions $\mathbf{v}_l \in L^2(\Omega;H^1_{per}(Y_l))$, $p_l \in L^2(\Omega \times Y_l)$, $\hat{\mathbf{v}}_l \in L^2(\hat{\Lambda};H^1(Z_l))$, and $\hat{p} \in L^2(\hat{\Lambda}\times Z)$ such that $\hat{\mathbf{v}}_l$ is $\hat{Z}-$periodic, $\hat{p}_l = \hat{p}|_{\hat{\Lambda}\times Z_l}$, and as $\varepsilon \to 0$*

$$
\begin{aligned}
&\mathbf{v}_l^\varepsilon \to \mathbf{v}_l,\ \ \varepsilon\nabla\mathbf{v}_l^\varepsilon \to \nabla_y \mathbf{v}_l, && p_l^\varepsilon = P_l^\varepsilon \chi_{\Omega_l^\varepsilon} \to p_l && \text{two-scale},\\
&\hat{\mathbf{v}}_l^\varepsilon \to \hat{\mathbf{v}}_l,\ \ \varepsilon\nabla\hat{\mathbf{v}}_l^\varepsilon \to \nabla_y \hat{\mathbf{v}}_l, && \hat{P}^\varepsilon \to \hat{p}, \quad \hat{p}_l^\varepsilon = \hat{P}^\varepsilon \chi_{\Lambda_l^\varepsilon} \to \hat{p}_l && \text{two-scale}.
\end{aligned}
$$

2. *There exist subsequences of $\{c_l^\varepsilon\}$ and $\{\hat{c}_j^\varepsilon\}$ (denoted again by $\{c_l^\varepsilon\}$, $\{\hat{c}_j^\varepsilon\}$) and $c_l \in L^2(0,T;H^1(\Omega))$, $\partial_t c_l \in L^2(\Omega_T)$, $c_l^1 \in L^2(\Omega_T;H^1_{per}(Y_l))$, $\hat{c}_j \in L^2(0,T;H^1(\hat{\Lambda}))$, $\hat{c}_j^1 \in L^2(\hat{\Lambda}_T;H^1(Z_j))$, and $\partial_t \hat{c}_j \in L^2(\hat{\Lambda}_T)$ such that $\hat{c}_j^1$ is $\hat{Z}-$periodic and as $\varepsilon \to 0$*

$$
\begin{aligned}
\mathcal{T}_\varepsilon^*(c_l^\varepsilon) &\rightharpoonup c_l && \text{weakly in } L^2(\Omega_T;H^1(Y_l))\ ,\\
\mathcal{T}_\varepsilon^*(c_l^\varepsilon) &\to c_l && \text{strongly in } L^2(0,T;L^2_{loc}(\Omega;H^1(Y_l))),\\
\partial_t\mathcal{T}_\varepsilon^*(c_l^\varepsilon) &\rightharpoonup \partial_t c_l && \text{weakly in } L^2(\Omega_T \times Y_l),\\
\mathcal{T}_\varepsilon^*(\nabla c_l^\varepsilon) &\rightharpoonup \nabla c_l + \nabla_y c_l^1 && \text{weakly in } L^2(\Omega_T \times Y_l),
\end{aligned}
\tag{46}
$$

$$
\begin{aligned}
\mathcal{T}_\varepsilon^{*,bl}(\hat{c}_j^\varepsilon) &\rightharpoonup \hat{c}_j && \text{weakly in } L^2(\hat{\Lambda}_T;H^1(Z_j)),\\
\mathcal{T}_\varepsilon^{*,bl}(\hat{c}_j^\varepsilon) &\to \hat{c}_j && \text{strongly in } L^2(0,T;L^2_{loc}(\hat{\Lambda};H^1(Z_j))),\\
\partial_t\mathcal{T}_\varepsilon^{*,bl}(\hat{c}_j^\varepsilon) &\rightharpoonup \partial_t \hat{c}_j && \text{weakly in } L^2(\hat{\Lambda}_T \times Z_j),\\
\mathcal{T}_\varepsilon^{*,bl}(\nabla \hat{c}_j^\varepsilon) &\rightharpoonup \nabla \hat{c}_j + \nabla_y \hat{c}_j^1 && \text{weakly in } L^2(\hat{\Lambda}_T \times Z_j),
\end{aligned}
\tag{47}
$$

and

$$\begin{aligned} \mathcal{T}_\varepsilon^b(c_l^\varepsilon) &\rightharpoonup c_l && \textit{weakly in } L^2(\Omega_T \times \Gamma_l), \\ \mathcal{T}_\varepsilon^{b,bl}(\hat{c}_j^\varepsilon) &\rightharpoonup \hat{c}_j && \textit{weakly in } L^2(\hat{\Lambda}_T \times R_{av}), \end{aligned} \tag{48}$$

where $l = a, v, s$ *and* $j = av, s$. *Here,* $\hat{c}_{av}^\varepsilon = \hat{c}_a^\varepsilon \chi_{\Lambda_a^\varepsilon} + \hat{c}_v^\varepsilon \chi_{\Lambda_v^\varepsilon}$, $\Gamma_s = \Gamma_a \cup \Gamma_v$, $R_{av} = R_a \cup R_v$, *and* $Z_{av} = \operatorname{Int}(\overline{Z}_a \cup \overline{Z}_v)$.

Sketch of proof. Due to the continuity of concentrations on Σ^ε, we can define $\hat{c}_{av}^\varepsilon = \hat{c}_a^\varepsilon \chi_{\Lambda_a^\varepsilon} + \hat{c}_v^\varepsilon \chi_{\Lambda_v^\varepsilon}$. The *a priori* estimates in (39), (40) and (41) along with (a) the compactness theorem for two-scale convergence, (b) related convergence results for unfolded sequences [3, 8, 22, 26, 27], and (c) Theorem 5.6 imply the convergence results in the statement of the lemma.

The last two convergence results in (48) follow from the weak convergence of $\mathcal{T}_\varepsilon^*(c_l^\varepsilon)$ and $\mathcal{T}_\varepsilon^{*,bl}(\hat{c}_j^\varepsilon)$ in $L^2(\Omega_T; H^1(Y_l))$ and $L^2(\hat{\Lambda}_T; H^1(Z_j))$, respectively, along with the trace theorem applied in $H^1(Y_l)$ and $H^1(Z_j)$, where $l = a, v, s$ and $j = av, s$. ■

6. Derivation of macroscopic equations for velocity fields

We now derive the homogenized, macroscopic equations for the arterial and venous blood velocity fields in the two tissue layers (skin tissue layer and fat tissue layer) of the adopted tissue geometry. We start with Theorem 2.1, which is the first of the main results of the paper.

Proof of Theorem 2.1. We first use the following test functions in (36):

(a) $\phi_l(x) = \varepsilon \psi_l\left(x, \frac{x}{\varepsilon}\right)$ with $\psi_l \in C_0^\infty(\Omega, C_{\text{per}}^\infty(Y))$ and $\psi_l(x, y) = 0$ on $\Omega \times \Gamma_l$, and
(b) $\hat{\phi}_l(x) = \varepsilon \hat{\psi}\left(\hat{x}, \frac{x}{\varepsilon}\right)$ with $\hat{\psi} \in C_0^\infty(\hat{\Lambda}, C_{per}^\infty(\hat{Z}; C_0^\infty(0,1)))$ and $\hat{\psi}(\hat{x}, y) = 0$ on $\hat{\Lambda} \times (R_a \cup R_v)$.

Using the derived *a priori* estimates and applying the two-scale convergence of p_a^ε, $\hat{p}_a^\varepsilon$, p_v^ε, and $\hat{p}_v^\varepsilon$, established in section 5, we obtain that

$$|Y|^{-1}\langle p_a, \operatorname{div}_y \psi_a \rangle_{\Omega \times Y_a} + |Y|^{-1}\langle p_v, \operatorname{div}_y \psi_v \rangle_{\Omega \times Y_v} + |\hat{Z}|^{-1}\langle \hat{p}, \operatorname{div}_y \hat{\psi} \rangle_{\hat{\Lambda} \times Z_{av}} = 0. \tag{49}$$

The last equation implies that

(a) $p_l \in L^2(\Omega; H^1(Y_l))$ with $\nabla_y p_l = 0$ a.e. in $\Omega \times Y_l$, and
(b) $\hat{p} \in L^2(\hat{\Lambda}; H^1(Z_{av}))$ with $\nabla_y \hat{p} = 0$ a.e. in $\hat{\Lambda} \times Z_{av}$,

where $l = a, v$. Thus, $p_a = p_a(x)$, $p_v = p_v(x)$ in Ω and $\hat{p} = \hat{p}(\hat{x})$ in $\hat{\Lambda}$.

The two-scale convergence of $\mathbf{v}_l^\varepsilon$ and $\hat{\mathbf{v}}_l^\varepsilon$ at the oscillating boundaries Γ_l^ε, R_l^ε, and $\Lambda_l^\varepsilon \cap \{x_n = \varepsilon\}$ is ensured by the *a priori* estimates (39) and the boundary estimate (44). This implies that

$$\mathbf{v}_l(x, y) = 0 \quad \text{on } \Omega \times \Gamma_l, \qquad \hat{\mathbf{v}}_l(x, y) = 0 \quad \text{on } \hat{\Lambda} \times (R_l \cup \hat{Z}_{av}^1), \quad l = a, v, \tag{50}$$

where $\hat{Z}_{av}^1 = \partial Z_{av} \cap \{y_n = 1\}$. Using $\operatorname{div} \mathbf{v}_l^\varepsilon = 0$ in Ω_l^ε and considering $\psi_l \in C_0^\infty(\Omega; C_{\text{per}}^\infty(Y))$, we obtain

$$0 = \langle \operatorname{div} \mathbf{v}_l^\varepsilon(x), \psi_l(x, x/\varepsilon) \rangle_{\Omega_l^\varepsilon} = -\langle \mathbf{v}_l^\varepsilon(x), \nabla \psi_l(x, x/\varepsilon) + 1/\varepsilon \nabla_y \psi_l(x, x/\varepsilon) \rangle_{\Omega_l^\varepsilon}.$$

The two-scale convergence of $\mathbf{v}_l^\varepsilon$ implies that

$$0 = \lim_{\varepsilon\to 0}\langle \mathbf{v}_l^\varepsilon(x), \nabla_y \psi_l(x, x/\varepsilon)\rangle_{\Omega_l^\varepsilon} = -|Y|^{-1}\langle \mathrm{div}_y \mathbf{v}_l(x,y), \psi_l(x,y)\rangle_{\Omega\times Y_l}. \tag{51}$$

Similarly, using $\mathrm{div}\,\hat{\mathbf{v}}_l^\varepsilon = 0$ in Λ_l^ε with $\hat{\mathbf{v}}_a^\varepsilon = \hat{\mathbf{v}}_v^\varepsilon$ on Σ^ε and $\hat\psi \in C_0^\infty(\hat\Lambda; C^\infty_{\mathrm{per}}(\hat Z; C_0^\infty(0,1)))$, we obtain

$$\begin{aligned}0 = \lim_{\varepsilon\to 0}\langle \mathrm{div}\,\hat{\mathbf{v}}_{av}^\varepsilon(x), \hat\psi(\hat x, x/\varepsilon)\rangle_{\Lambda_{av}^\varepsilon} &= -|\hat Z|^{-1}\langle \hat{\mathbf{v}}_{av}(\hat x, y), \nabla_y \hat\psi(\hat x, y)\rangle_{\hat\Lambda\times Z_{av}} \\ &= |\hat Z|^{-1}\langle \mathrm{div}_y \hat{\mathbf{v}}_{av}(\hat x, y), \hat\psi(\hat x, y)\rangle_{\hat\Lambda\times Z_{av}},\end{aligned}$$

where $\Lambda_{av}^\varepsilon = \Lambda_a^\varepsilon \cup \Sigma^\varepsilon \cup \Lambda_v^\varepsilon$. Therefore, $\mathrm{div}_y \mathbf{v}_l = 0$ in $\Omega \times Y_l$ and $\mathrm{div}_y \hat{\mathbf{v}}_{av} = 0$ in $\hat\Lambda \times Z_{av}$, where $l = a, v$.

We now consider the normal velocity $\hat{\mathbf{v}}_l^\varepsilon \cdot \mathbf{n}$ on $\hat\Lambda \cap \partial\Lambda_l^\varepsilon$. The transmission conditions (26) yield

$$\begin{aligned}\langle \hat{\mathbf{v}}_l^\varepsilon \cdot \mathbf{n}, \hat\psi(\hat x, \hat x/\varepsilon, 0)\rangle_{\hat\Lambda\cap\partial\Lambda_l^\varepsilon} &= \varepsilon\langle \mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \psi(\hat x, 0, \hat x/\varepsilon, 0)\rangle_{\hat\Lambda\cap\partial\Lambda_l^\varepsilon} \\ &= \varepsilon\langle \mathrm{div}\mathbf{v}_l^\varepsilon, \psi(x, x/\varepsilon)\rangle_{\Omega_l^\varepsilon} + \varepsilon\langle \mathbf{v}_l^\varepsilon, \nabla\psi(x, x/\varepsilon)\rangle_{\Omega_l^\varepsilon},\end{aligned}$$

where $\hat\psi \in C^\infty(\overline{\hat\Lambda}; C^\infty_{\mathrm{per}}(\hat Z; C^\infty[0,1]))$, $\psi \in C^\infty(\overline\Omega; C^\infty_{\mathrm{per}}(Y))$ with $\psi = 0$ on $\Gamma_D \times Y$, and $\hat\psi(\hat x, \hat x/\varepsilon, 0) = \psi(\hat x, 0, \hat x/\varepsilon, 0)$ on $\hat\Lambda$. Then using $\mathrm{div}\mathbf{v}_l^\varepsilon = 0$ in Ω_l^ε and $\mathrm{div}_y \mathbf{v}_l = 0$ in $\Omega \times Y_l$, along with the two-scale convergence of $\mathbf{v}_l^\varepsilon$ and $\hat{\mathbf{v}}_l^\varepsilon$, implies

$$|\hat Z|^{-1}\langle \hat{\mathbf{v}}_l \cdot \mathbf{n}, \hat\psi(\hat x, \hat y, 0)\rangle_{\hat\Lambda\times \hat Z_l^0} = |Y|^{-1}\langle \mathbf{v}_l, \nabla_y \psi(x,y)\rangle_{\Omega\times Y_l} = 0.$$

Hence, $\hat{\mathbf{v}}_l \cdot \mathbf{n} = 0$ on $\hat\Lambda \times \hat Z_l^0$, where $\hat Z_l^0 = \partial Z_l \cap \{y_n = 0\}$.

Using $\mathrm{div}\,\mathbf{v}_l^\varepsilon = 0$ in Ω_l^ε and taking $\psi \in C^\infty(\overline\Omega)$ yield

$$0 = \lim_{\varepsilon\to 0}\langle \mathrm{div}\,\mathbf{v}_l^\varepsilon, \psi\rangle_{\Omega_l^\varepsilon} = \lim_{\varepsilon\to 0}\Big[-\langle \mathbf{v}_l^\varepsilon, \nabla\psi\rangle_{\Omega_l^\varepsilon} + \langle \mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \psi\rangle_{\partial\Omega_l^\varepsilon \cap(\Gamma_D\cup\hat\Lambda)}\Big]. \tag{52}$$

Applying two-scale convergence in the first term on the right-hand side of (52) and integrating by parts imply

$$\begin{aligned}-\Big\langle \mathrm{div}\Big[\frac{1}{|Y|}\int_{Y_l}\mathbf{v}_l(\cdot, y)dy\Big], \psi\Big\rangle_\Omega + \Big\langle \frac{1}{|Y|}\int_{Y_l}\mathbf{v}_l(\cdot,y)dy\cdot\mathbf{n},\ \psi\Big\rangle_{\partial\Omega} \\ = \lim_{\varepsilon\to 0}\langle \mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \psi\rangle_{\partial\Omega_l^\varepsilon\cap(\Gamma_D\cup\hat\Lambda)}.\end{aligned} \tag{53}$$

Since $C_0^\infty(\Omega)$ is dense in $L^2(\Omega)$, the last equation yields

$$\mathrm{div}\left(\frac{1}{|Y|}\int_{Y_l}\mathbf{v}_l(x,y)dy\right) = 0 \qquad \text{a.e. in } \ \Omega, \quad \text{for } \ l = a, v. \tag{54}$$

Taking $\psi \in C^\infty(\overline\Omega)$ with $\psi(x) = 0$ on $\Gamma_D \cup \hat\Lambda$ in (53), and using the calculations above, we obtain

$$\Big(\frac{1}{|Y|}\int_{Y_l}\mathbf{v}_l(\cdot,y)dy\Big)\cdot\mathbf{n} = 0 \qquad \text{on } \ \partial\hat\Omega \times (-L, 0). \tag{55}$$

Similarly, taking $\psi \in C^\infty(\overline{\Omega})$ with $\psi(x) = 0$ on $\hat{\Lambda}$ in (53) we obtain

$$\lim_{\varepsilon\to 0}\langle \mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \psi\rangle_{\partial\Omega_l^\varepsilon\cap\Gamma_D} = \Big\langle \frac{1}{|Y|}\int_{Y_l} \mathbf{v}_l(\cdot, y)dy\cdot \mathbf{n}, \psi\Big\rangle_{\Gamma_D}. \tag{56}$$

These calculations imply that

$$\lim_{\varepsilon\to 0}\langle \mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \psi\rangle_{\partial\Omega_l^\varepsilon\cap\hat{\Lambda}} = \Big\langle \frac{1}{|Y|}\int_{Y_l} \mathbf{v}_l(\cdot, y)dy\cdot \mathbf{n},\, \psi\Big\rangle_{\hat{\Lambda}} \qquad \text{for} \quad \psi \in C^\infty(\overline{\Omega}). \tag{57}$$

We now consider a test function $\hat{\phi} \in C^\infty(\Lambda^\varepsilon)$, such that $\hat{\phi}$ is constant in x_n and $\hat{\phi}(x) = 0$ on $\partial\hat{\Omega}\times(0,\varepsilon)$. Applying $\operatorname{div}\hat{\mathbf{v}}_l^\varepsilon(x) = 0$ in Λ_l^ε with $\hat{\mathbf{v}}_l^\varepsilon(x) = 0$ on the boundaries R_l^ε, $(\partial\hat{\Omega}\times(0,\varepsilon))\cap\partial\Lambda_l^\varepsilon$, and $(\hat{\Omega}\times\{\varepsilon\})\cap\partial\Lambda_l^\varepsilon$, along with $\hat{\mathbf{v}}_a^\varepsilon = \hat{\mathbf{v}}_v^\varepsilon$ on Σ^ε, yields

$$0 = \lim_{\varepsilon\to 0}\frac{1}{\varepsilon}\langle \operatorname{div}\hat{\mathbf{v}}_{av}^\varepsilon, \hat{\phi}\rangle_{\Lambda_{av}^\varepsilon} = \lim_{\varepsilon\to 0}\big(-\frac{1}{\varepsilon}\langle\hat{\mathbf{v}}_{av}^\varepsilon, \nabla_{\hat{x}}\hat{\phi}\rangle_{\Lambda_{av}^\varepsilon} + \frac{1}{\varepsilon}\langle\hat{\mathbf{v}}_{av}^\varepsilon\cdot\hat{\mathbf{n}}, \hat{\phi}\rangle_{\partial\Lambda_{av}^\varepsilon\cap\hat{\Lambda}}\big), \tag{58}$$

where $\hat{\mathbf{v}}_{av}^\varepsilon = \hat{\mathbf{v}}_a^\varepsilon\chi_{\Lambda_a^\varepsilon} + \hat{\mathbf{v}}_v^\varepsilon\chi_{\Lambda_v^\varepsilon}$. The transmission condition $\frac{1}{\varepsilon}\hat{\mathbf{v}}_l^\varepsilon\cdot\hat{\mathbf{n}} = \mathbf{v}_l^\varepsilon\cdot\hat{\mathbf{n}}$ on $\hat{\Lambda}\cap\partial\Omega_l^\varepsilon$ along with the two-scale convergence of $\hat{\mathbf{v}}_l^\varepsilon$ and the convergence in (57) imply

$$|\hat{Z}|^{-1}\langle\hat{\mathbf{v}}_{av}, \nabla_{\hat{x}}\hat{\phi}\rangle_{\hat{\Lambda}\times Z_{av}} = \langle |Y|^{-1}\mathbf{v}_a\cdot\hat{\mathbf{n}},\, \hat{\phi}\rangle_{\hat{\Lambda}\times Y_a} + \langle |Y|^{-1}\mathbf{v}_v\cdot\hat{\mathbf{n}},\, \hat{\phi}\rangle_{\hat{\Lambda}\times Y_v},$$

where $\hat{\mathbf{n}}$ is the external normal vector to $\partial\Lambda^\varepsilon\cap\hat{\Lambda}$. Thus

$$\operatorname{div}_{\hat{x}}\Big(\frac{1}{|\hat{Z}|}\int_{Z_{av}}\hat{\mathbf{v}}_{av}\,dy\Big) = \frac{1}{|Y|}\int_{Y_a}\mathbf{v}_a\,dy\cdot\mathbf{n} + \frac{1}{|Y|}\int_{Y_v}\mathbf{v}_v\,dy\cdot\mathbf{n} \quad \text{on} \quad \hat{\Lambda}, \tag{59}$$

where $\mathbf{n}$ is the external normal vector to $\partial\Omega\cap\hat{\Lambda}$, and

$$\frac{1}{|\hat{Z}|}\int_{Z_{av}}\hat{\mathbf{v}}_{av}(x,y)dy\cdot\mathbf{n} = 0 \qquad \text{for} \quad x\in\partial\hat{\Lambda}.$$

Considering $\mathbf{v}^\varepsilon = \mathbf{v}_a^\varepsilon\chi_{\Omega_a^\varepsilon} + \mathbf{v}_v^\varepsilon\chi_{\Omega_v^\varepsilon} + \varepsilon^{-1}\hat{\mathbf{v}}_a^\varepsilon\chi_{\Lambda_a^\varepsilon} + \varepsilon^{-1}\hat{\mathbf{v}}_v^\varepsilon\chi_{\Lambda_v^\varepsilon}$ we obtain

$$0 = \int_{\Omega_{av}^\varepsilon\cup\Lambda_{av}^\varepsilon}\operatorname{div}\mathbf{v}^\varepsilon dx = \int_{\Gamma_D\cap\partial\Omega_a^\varepsilon}\mathbf{v}_a^\varepsilon\cdot\mathbf{n}\,d\hat{x} + \int_{\Gamma_D\cap\partial\Omega_v^\varepsilon}\mathbf{v}_v^\varepsilon\cdot\mathbf{n}\,d\hat{x},$$

where $\Omega_{av}^\varepsilon = \Omega_a^\varepsilon\cup\Omega_v^\varepsilon$. Then the convergence in (56) yields

$$\frac{1}{|Y|}\int_{\Gamma_D}\Big[\int_{Y_a}\mathbf{v}_a(\cdot,y)dy + \int_{Y_v}\mathbf{v}_v(\cdot,y)dy\Big]\cdot\mathbf{n}\,d\hat{x} = 0. \tag{60}$$

Considering $\operatorname{div}\big(\int_{Y_a}\mathbf{v}_a dy + \int_{Y_v}\mathbf{v}_v dy\big) = 0$ in Ω and using (60) imply

$$\int_{\hat{\Lambda}}\Big[\int_{Y_a}\mathbf{v}_a(\cdot,y)\,dy + \int_{Y_v}\mathbf{v}_v(\cdot,y)\,dy\Big]\cdot\mathbf{n}\,d\hat{x} = 0. \tag{61}$$

We now consider functions ψ_l and $\hat{\psi}$ such that

(a) $\psi_l \in C^\infty(\overline{\Omega}; C^\infty_{\rm per}(Y))$, $\mathrm{div}_y \psi_l = 0$ in $\Omega\times Y$, $\psi_l = 0$ on $(\partial\hat{\Omega}\times(-L,0)\cup\Gamma_D)\times Y$ and on $\Omega\times\Gamma_l$,
(b) $\hat\psi \in C^\infty_0(\hat\Lambda; C^\infty_{\rm per}(\hat Z; C^\infty[0,1]))$, $\mathrm{div}_y\hat\psi = 0$ in $\hat\Lambda\times Z$, $\hat\psi = 0$ on $\hat\Lambda\times(R_{av}\cup\hat Z^1_{av})$.

Then we choose $\phi_l(x) = \psi_l(x, \frac{x}{\varepsilon})$ and $\hat\phi_l(x) = \hat\psi(x, \frac{x}{\varepsilon})$, $l = a, v$, as test functions in (36). The two-scale convergence of $(\mathbf{v}^\varepsilon_l, p^\varepsilon_l)$ and $(\hat{\mathbf{v}}^\varepsilon_l, \hat p^\varepsilon_l)$, with $l = a, v$, implies

$$\begin{aligned}&\frac{1}{|Y|}\sum_{l=a,v}\Big(\langle 2\mu S_y\mathbf{v}_l, S_y\psi_l\rangle_{\Omega\times Y_l} - \langle p_l, \mathrm{div}_x\psi_l\rangle_{\Omega\times Y_l} - \frac{1}{L}\langle p^0_l, \psi_{l,n}\rangle_{\Omega\times Y_l}\Big)\\&+\frac{1}{|\hat Z|}\Big(\langle 2\mu S_y\hat{\mathbf{v}}_{av}, S_y\hat\psi\rangle_{\hat\Lambda\times Z_{av}} - \langle\hat p, \mathrm{div}_{\hat x}\hat\psi\rangle_{\hat\Lambda\times Z_{av}}\Big) = 0.\end{aligned}\tag{62}$$

We consider functions ψ_l and $\hat\psi$ such that

(a) $\psi_l \in C^\infty_0(\Omega, C^\infty_{\rm per}(Y))$ with $\mathrm{div}_y\psi_l = 0$, $\psi_l = 0$ on $\Omega\times\Gamma_l$, and
(b) $\hat\psi \in C^\infty_0(\hat\Lambda, C^\infty_{\rm per}(\hat Z; C^\infty_0(0,1)))$ with $\mathrm{div}_y\hat\psi = 0$, $\mathrm{div}_{\hat x}\langle\hat\psi, 1\rangle_{Z_{av}} = 0$, and $\hat\psi(\hat x, y) = 0$ on $\hat\Lambda\times R_{av}$.

Using the characterization of the orthogonal complement to the space of divergence-free functions (see, e.g., [16]), we obtain the existence of $p^1_l \in L^2(\Omega\times Y_l)/\mathbb{R}$, $\hat p^1_{av}\in L^2(\hat\Lambda\times Z_{av})/\mathbb{R}$, and $\tilde p \in H^1(\hat\Lambda)/\mathbb{R}$ such that

$$\begin{aligned}&-\mu\Delta_y\mathbf{v}_l + \nabla_x p_l + \nabla_y p^1_l = \frac{1}{L}p^0_l\,\mathbf{e}_n && \text{in } \Omega\times Y_l, && l = a, v,\\&-\mu\Delta_y\hat{\mathbf{v}}_{av} + \nabla_{\hat x}\tilde p + \nabla_y\hat p^1_{av} = 0 && \text{in } \hat\Lambda\times Z_{av}.\end{aligned}\tag{63}$$

Combining equations (63) and (62), and considering $\hat\psi \in C^\infty(\overline{\hat\Lambda}; C^\infty_{\rm per}(\hat Z; C^\infty[0,1]))$ with $\mathrm{div}_y\hat\psi = 0$ in $\hat\Lambda\times Z$, $\langle\hat\psi, 1\rangle_{Z_{av}}\cdot\mathbf{n} = 0$ on $\partial\hat\Lambda$, and $\hat\psi = 0$ on $\hat\Lambda\times(R_{av}\cup\hat Z^0_{av}\cup\hat Z^1_{av})$, we obtain

$$|\hat Z|^{-1}\langle\hat p - \tilde p, \mathrm{div}_{\hat x}\hat\psi\rangle_{\hat\Lambda\times Z_{av}} + |Y|^{-1}\langle p_a, \psi\cdot\mathbf{n}\rangle_{\hat\Lambda\times Y_a} + |Y|^{-1}\langle p_v, \psi\cdot\mathbf{n}\rangle_{\hat\Lambda\times Y_v} = 0.$$

Thus using equality (59) we obtain $p_a = p_v = \hat p$ and $\tilde p = 2\hat p$ on $\hat\Lambda$.

Relaxing now the assumptions on $\hat\psi$ and using $\hat\psi\cdot\mathbf{n} = 0$ on $\hat\Lambda\times\hat Z^0_{av}$ imply

$$(2\mu\,\mathrm{S}_y\hat{\mathbf{v}}_{av} - \hat p^1_{av}I)\,\mathbf{n}\times\mathbf{n} = 0 \qquad \text{on } \hat\Lambda\times\hat Z^0_{av}.$$

Setting $\bar p_l = p_l - p^0_l\frac{x_n}{L}$ and omitting the bar for the sake of clarity, we obtain the two-scale model

$$\begin{aligned}&-\mu\Delta_y\mathbf{v}_l + \nabla_x p_l + \nabla_y p^1_l = 0, \qquad \mathrm{div}_y\mathbf{v}_l = 0 \quad \text{in } \Omega\times Y_l, \quad l = a, v\\&\qquad\mathbf{v}_l = 0 \quad \text{on } \Omega\times\Gamma_l, \qquad \mathbf{v}_l,\ p^1_l \quad \text{are } Y-\text{periodic},\\&\quad p_l = p^0_l \quad \text{on } \Gamma_D\times Y_l\end{aligned}\tag{64}$$

and

$$
\begin{aligned}
& -\mu\Delta_y \hat{\mathbf{v}}_{av} + 2\nabla_{\hat{x}}\hat{p} + \nabla_y \hat{p}^1_{av} = 0, && \mathrm{div}_y \hat{\mathbf{v}}_{av} = 0 && \text{in } \hat{\Lambda}\times Z_{av}, \\
& (2\mu S_y \hat{\mathbf{v}}_{av} - \hat{p}^1_{av} I)\,\mathbf{n}\times\mathbf{n} = 0, && \hat{\mathbf{v}}_{av}\cdot\mathbf{n} = 0 && \text{on } \hat{\Lambda}\times \hat{Z}^0_{av}, \\
& \hat{\mathbf{v}}_{av} = 0 \qquad \text{on } \hat{\Lambda}\times(R_{av}\cup \hat{Z}^1_{av}), && \hat{\mathbf{v}}_{av},\, \hat{p}^1_{av} && \text{are } \hat{Z}-\text{periodic.}
\end{aligned}
\tag{65}
$$

Finally, for $(x, y) \in \Omega \times Y_l$ and $(\hat{x}, y) \in \hat{\Lambda} \times Z_{av}$, we consider the ansatz

$$
\begin{aligned}
\mathbf{v}_l(x,y) &= -\sum_{j=1}^{n} \partial_{x_j} p_l(x)\omega_l^j(y), & p^1_l(x,y) &= -\sum_{j=1}^{n} \partial_{x_j} p_l(x)\pi_l^j(y), \\
\hat{\mathbf{v}}_{av}(\hat{x},y) &= -2\sum_{j=1}^{n-1} \partial_{x_j} \hat{p}(\hat{x})\hat{\omega}^j(y), & \hat{p}^1_{av}(\hat{x},y) &= -2\sum_{j=1}^{n-1} \partial_{x_j} \hat{p}(\hat{x})\hat{\pi}^j(y),
\end{aligned}
\tag{66}
$$

where $l = a, v$, and (ω_l^j, π_l^j), $(\hat{\omega}^j, \hat{\pi}^j)$ are solutions of the unit cell problems (2) and (3) respectively. Applying the ansatz (66) to equations (64) and (65), and using equations (54) and (59), yields the macroscopic equations (10) and (11) for $\mathbf{v}_l^0(\cdot) = \frac{1}{|Y|}\int_{Y_l} \mathbf{v}_l(\cdot, y)dy$, p_l, $\hat{\mathbf{v}}^0_{av}(\cdot) = \frac{1}{|\hat{Z}|}\int_{Z_{av}} \hat{\mathbf{v}}_{av}(\cdot, y)dy$, and $\hat{p}$. The integral condition in (61) ensures the well-posedness of the macroscopic model (11). Considering the differences of two solutions $p_l^1 - p_l^2$ and $\hat{p}^1 - \hat{p}^2$ of (10) and (11), and using the Dirichlet boundary conditions on Γ_D and the continuity conditions on $\hat{\Lambda}$, we obtain the uniqueness of the solution of the macroscopic model. ■

7. Derivation of macroscopic equations for oxygen concentrations

In this section, we continue our derivation of the homogenized equations for the microscopic system (22)–(35) by turning our attention to the oxygen concentrations in arterial blood, venous blood, and tissue. Theorem 2.2 provides the macroscopic equations dictating the dynamics of the various oxygen concentrations as $\varepsilon \to 0$, and it complements Theorem 2.1 that was proven in the previous section. For the remainder of this section, we define $\hat{\mathbf{v}}_{av}(\hat{x}, y) = \hat{\mathbf{v}}_a(\hat{x}, y)\chi_{Z_a}(y) + \hat{\mathbf{v}}_v(\hat{x}, y)\chi_{Z_v}(y)$ for a.a. $(\hat{x}, y) \in \hat{\Lambda} \times Z_{av}$.

Proof of Theorem 2.2. We consider $\psi_l(t, x) = \phi_l^1(t, x) + \varepsilon\phi_l^2(t, x, \frac{x}{\varepsilon})$, for $l = a, v$, and $\hat{\psi}(t, x) = \hat{\phi}_1(t, \hat{x}) + \varepsilon\hat{\phi}_2(t, \hat{x}, \frac{x}{\varepsilon})$ as test functions in (37), where

(a) $\phi_l^1 \in C^\infty(\overline{\Omega}_T) \cap L^2(0, T; W(\Omega))$ with $\phi_l^1(t, \hat{x}, 0) = \hat{\phi}_1(t, \hat{x})$ in $\hat{\Lambda}_T$, and $\phi_l^2 \in C_0^\infty(\Omega_T; C_{per}(Y))$

(b) $\hat{\phi}_1 \in C^\infty(\overline{\hat{\Lambda}_T})$ and $\hat{\phi}_2 \in C_0^\infty(\hat{\Lambda}_T; C^\infty_{per}(\hat{Z}; C_0^\infty(0, 1)))$.

Considering $\Omega^\delta = \{x \in \Omega : \mathrm{dist}(x, \partial\Omega) > \delta\}$ and $\tilde{\Omega}_l^{\varepsilon,\delta} = \{x \in \Omega_l^\varepsilon : \mathrm{dist}(x, \partial\Omega_l^\varepsilon) > \delta\}$ we can write

$$
\langle \mathbf{v}_l^\varepsilon c_l^\varepsilon, \nabla\psi_l\rangle_{\Omega^\varepsilon_{l,T}} = \frac{1}{|Y|}\langle \mathcal{T}^*_\varepsilon(\mathbf{v}_l^\varepsilon)\mathcal{T}^*_\varepsilon(c_l^\varepsilon), \mathcal{T}^*_\varepsilon(\nabla\psi_l)\rangle_{\Omega^\delta_T\times Y_l} + \langle \mathbf{v}_l^\varepsilon c_l^\varepsilon, \nabla\psi_l\rangle_{\tilde{\Omega}^{\varepsilon,\delta}_{l,T}} .
$$

Due to the boundedness of c_l^ε and the *a priori* estimates for $\mathbf{v}_l^\varepsilon$, we obtain

$$|\langle \mathbf{v}_l^\varepsilon c_l^\varepsilon, \nabla \psi_l\rangle_{\tilde\Omega^{\varepsilon,\delta}_{l,T}}| \leq C\|\mathbf{v}_l^\varepsilon\|_{L^2(\tilde\Omega_l^{\varepsilon,\delta})}\Big[\|\nabla\phi_l^1\|_{L^2(\tilde\Omega_T^\delta)} + \varepsilon\|\nabla\phi_l^2\|_{L^2(\tilde\Omega_T^\delta\times Y_l)} \\ +\|\nabla_y \phi_l^2\|_{L^2(\tilde\Omega_T^\delta\times Y_l)}\Big] \to 0 \quad \text{as} \quad \delta\to 0\ ,$$

where $\tilde\Omega^\delta = \{x\in\Omega : \operatorname{dist}(x,\partial\Omega)<\delta\}$. Applying the weak convergence of $\mathcal{T}_\varepsilon^*(\mathbf{v}_l^\varepsilon)$, the strong convergence of $\mathcal{T}_\varepsilon^*(\nabla\psi_l)$, the local strong convergence of $\mathcal{T}_\varepsilon^*(c_l^\varepsilon)$, and letting $\varepsilon\to 0$ and $\delta\to 0$ in that order, we obtain

$$\langle \mathbf{v}_l^\varepsilon c_l^\varepsilon, \nabla\psi_l\rangle_{\Omega^\varepsilon_{l,T}} \to 1/|Y|\langle \mathbf{v}_l c_l, \nabla\phi_l^1 + \nabla_y\phi_l^2\rangle_{\Omega_T\times Y_l}\ .$$

In a similar way as for $\mathbf{v}_l^\varepsilon$, the regularity of $\hat\psi$ and the *a priori* estimates and convergence results for $\hat{\mathbf{v}}_{av}^\varepsilon$ and $\hat c_l^\varepsilon$ imply

$$\frac{1}{\varepsilon}\langle \hat{\mathbf{v}}^\varepsilon_{av}\hat c^\varepsilon_{av}, \nabla\hat\psi\rangle_{\Lambda^\varepsilon_{av},T} \to |\hat Z|^{-1}\langle \hat{\mathbf{v}}_{av}\hat c, \nabla\hat\phi_1 + \nabla_y\hat\phi_2\rangle_{\hat\Lambda_T\times Z_{av}} \quad \text{as} \quad \varepsilon\to 0 \ \text{ and } \ \delta\to 0.$$

The weak convergence of $\mathcal{T}_\varepsilon^*(c_l^\varepsilon)$ and $\mathcal{T}_\varepsilon^*(\nabla c_l^\varepsilon)$, in conjunction with the strong convergence of $\mathcal{T}_\varepsilon^*(\psi_l)$ and $\mathcal{T}_\varepsilon^*(\nabla\psi_l)$, imply the convergence of $\langle\partial_t c_l^\varepsilon, \psi_l\rangle_{\Omega_l^\varepsilon,T}$ and $\langle D_l^\varepsilon\nabla c_l^\varepsilon, \nabla\psi_l\rangle_{\Omega_l^\varepsilon,T}$. Similar arguments pertaining to the unfolding operator $\mathcal{T}_\varepsilon^{*,bl}$ and the convergence results for unfolded sequences prove the convergence of $\dfrac{1}{\varepsilon}\langle\partial_t\hat c_l^\varepsilon, \hat\psi\rangle_{\Lambda_l^\varepsilon,T}$ and $\dfrac{1}{\varepsilon}\langle\hat D_l^\varepsilon\nabla\hat c_l^\varepsilon, \nabla\hat\psi\rangle_{\Lambda_l^\varepsilon,T}$. The weak convergence of $\mathcal{T}_\varepsilon^*(c_l^\varepsilon)$ in $L^2(\Omega_T\times\Gamma_l)$ and of $\mathcal{T}_\varepsilon^{*,bl}(\hat c_l^\varepsilon)$ in $L^2(\hat\Lambda_T\times R_l)$ (shown in Lemma 5.7) ensure the convergence of integrals over Γ_l^ε and R_l^ε.

Thus, we obtain the macroscopic equations

$$\frac{1}{|Y|}\sum_{l=a,v}\big[\langle\partial_t c_l, \phi_l^1\rangle_{\Omega_T\times Y_l} + \langle D_l(y)(\nabla c_l + \nabla_y c_l^1) - \mathbf{v}_l c_l, \nabla\phi_l^1 + \nabla_y\phi_l^2\rangle_{\Omega_T\times Y_l}\big] \\ +\frac{1}{|\hat Z|}\Big[\langle\partial_t\hat c, \hat\phi_1\rangle_{\hat\Lambda_T\times Z_{av}} + \langle\hat D_{av}(y)(\nabla_{\hat x}\hat c + \nabla_y\hat c^1) - \hat{\mathbf{v}}_{av}\hat c, \nabla_{\hat x}\hat\phi_1 + \nabla_y\hat\phi_2\rangle_{\hat\Lambda_T\times Z_{av}}\Big] \\ = \frac{1}{|Y|}\sum_{l=a,v}\langle\lambda_l(c_s - c_l), \phi_l^1\rangle_{\Omega_T\times\Gamma_l} + \frac{1}{|\hat Z|}\sum_{l=a,v}\langle\hat\lambda_l(\hat c_s - \hat c), \hat\phi_1\rangle_{\hat\Lambda_T\times R_l}.$$

Furthermore, setting $\phi_l^1(t,x)=0$ in Ω_T, with $l=a,v$, and $\hat\phi_1(t,\hat x)=0$ in $\hat\Lambda_T$ we obtain

$$\frac{1}{|Y|}\sum_{l=a,v}\langle D_l(y)(\nabla c_l + \nabla_y c_l^1) - \mathbf{v}_l c_l, \nabla_y\phi_l^2\rangle_{\Omega_T\times Y_l} \\ +\frac{1}{|\hat Z|}\langle\hat D_{av}(y)(\nabla_{\hat x}\hat c + \nabla_y\hat c^1) - \hat{\mathbf{v}}_{av}\hat c, \nabla_y\hat\phi_2\rangle_{\hat\Lambda_T\times Z_{av}} = 0. \tag{67}$$

We now employ the divergence-free property of the velocity fields in $\Omega\times Y_l$ and $\hat\Lambda\times Z_{av}$ and the zero-boundary conditions on Γ_l and $R_l\cup Z^0_{av}\cup Z^1_{av}$. These, and the fact that c_l and $\hat{c}_{av}$ are independent of y, yield

$$\begin{aligned}
&\langle \mathbf{v}_l c_l, \nabla_y \phi_l^2 \rangle_{\Omega_T\times Y_l} = -\langle \mathrm{div}_y(\mathbf{v}_l\, c_l), \phi_l^2\rangle_{\Omega_T\times Y_l} + \langle \mathbf{v}_l\cdot \mathbf{n}\, c_l, \phi_l^2\rangle_{\Omega_T\times \partial Y_l} = 0, \quad l = a, v,\\
&\langle \hat{\mathbf{v}}_{av}\hat{c}, \nabla_y \hat{\phi}_2\rangle_{\hat\Lambda_T\times Z_{av}} = -\langle \mathrm{div}_y(\hat{\mathbf{v}}_{av}\, \hat{c}), \hat\phi_2\rangle_{\hat\Lambda_T\times Z_{av}} + \langle \hat{\mathbf{v}}_{av}\cdot \mathbf{n}\, \hat{c}, \hat\phi_2\rangle_{\hat\Lambda_T\times \partial Z_{av}} = 0.
\end{aligned}$$

Thus, taking first $\hat\phi_2(t,\hat x, y) = 0$ in $\hat\Lambda_T \times Z$ and $\phi_l^2 \in C_0^\infty(\Omega_T; C^\infty_{\text{per}}(Y))$ with $\phi_l^2(t,x,y) = 0$ for $y \in Y\setminus Y_l$, $(t,x)\in\Omega_T$, and then $\hat\phi_2 \in C_0^\infty(\hat\Lambda_T; C^\infty_{per}(\hat Z; C_0^\infty(0,1)))$ in (67), we have

$$\begin{aligned}
&\langle D_l(y)(\nabla c_l + \nabla_y c_l^1), \nabla_y\phi_l^2\rangle_{\Omega_T\times Y_l} = 0 \qquad \text{for} \quad l = a, v,\\
&\langle \hat D_{av}(y)(\nabla_{\hat x}\hat c + \nabla_y \hat c^1), \nabla_y\hat\phi_2\rangle_{\hat\Lambda_T\times Z_{av}} = 0.
\end{aligned}$$

Using the linearity of the equations above, we consider the ansatz

$$c_l^1(t,x,y) = \sum_{j=1}^n \partial_{x_j} c_l(t,x) w_l^j(y) \quad \text{for} \quad l = a, v, \quad \hat c^1(t,\hat x, y) = \sum_{j=1}^{n-1}\partial_{x_j}\hat c(t,\hat x)\hat w^j_{av}(y),$$

where w_l^j and $\hat w^j_{av}$ are solutions of the unit cell problems (5) and (6) respectively.

Then for $\phi_l^2 = 0$ and $\hat\phi_2 = 0$, and using the ansatz for c_l^1 and $\hat c^1$, we obtain

$$\begin{aligned}
&\sum_{l=a,v}\int_{\Omega_T}\left(\frac{|Y_l|}{|Y|}\partial_t c_l\, \phi_l^1 + (\mathcal{A}_l\nabla c_l - \mathbf{v}_l^0 c_l)\nabla\phi_l^1 - \lambda_l\frac{|\Gamma_l|}{|Y|}(c_s - c_l)\phi_l^1\right) dxdt\\
&+\int_{\hat\Lambda_T}\left(\frac{|Z_{av}|}{|\hat Z|}\partial_t\hat c\,\hat\phi_1 + (\hat{\mathcal{A}}_{av}\nabla_{\hat x}\hat c - \hat{\mathbf{v}}^0_{av}\hat c)\nabla_{\hat x}\hat\phi_1 - \sum_{l=a,v}\hat\lambda_l\frac{|R_l|}{|\hat Z|}(\hat c_s - \hat c)\hat\phi_1\right) d\hat x dt = 0,
\end{aligned}$$

where $\mathcal{A}_l$, $\mathbf{v}_l^0$, $\hat{\mathcal{A}}_{av}$ and $\hat{\mathbf{v}}^0_{av}$ are defined in (4) and (14). From the continuity conditions (33), we obtain $c_a(t,\hat x, 0) = \hat c(t,\hat x)$, $c_v(t,\hat x,0) = \hat c(t,\hat x)$ on $\hat\Lambda_T$. Considering $\phi_l^1 \in C_0^\infty(\Omega_T)$ and $\hat\phi_1 = 0$ and integrating by parts result in the macroscopic equations for c_a and c_v in (12)-(13). Considering

(a) $\hat\phi_1 \in C_0^\infty(\hat\Lambda_T)$, $\phi_l^1 \in C^\infty(\overline{\Omega}_T)$ with $\phi_l^1(t,x) = 0$ on Γ_D and $\phi_l^1(t,\hat x, 0) = \hat\phi_1(t,\hat x)$ on $\hat\Lambda_T$, and

(b) $\hat\phi_1 \in C^\infty(\overline{\hat\Lambda}_T)$, $\phi_l^1 \in C^\infty(\overline{\Omega}_T)$ with $\phi_l^1(t,x) = 0$ on Γ_D and $\phi_l^1(t,\hat x,0) = \hat\phi_1(t,\hat x)$ on $\hat\Lambda_T$,

in that order, and integrating by parts result in the macroscopic equation for $\hat c$ in (12)-(13). Similar arguments imply the macroscopic equations for c_s and $\hat c_s$. The assumptions on the initial conditions ensure the existence of $\hat c^0, \hat c^0_s \in H^1(\hat\Lambda)$ such that $\hat c^{\varepsilon,0} \to \hat c^0$, $\hat c_s^{\varepsilon,0} \to \hat c_s^0$ in the two-scale sense. This and the two-scale convergence of $\partial_t c_l^\varepsilon$, $\partial_t\hat c^\varepsilon$ and $\partial_t \hat c_s^\varepsilon$ imply that c_l, $\hat c$ and $\hat c_s$ satisfy the initial conditions, where $l = a, v, s$. Considering the equations for the difference of two solutions of the macroscopic problem (12)-(13) yields the uniqueness of the solutions. Finally, taking c_l^-, $\hat c^-$, $\hat c_s^-$, $(c_l - A)^+$, $(\hat c - A)^+$ and $(\hat c_s - A)^+$, for some $A \geq \max_{l=a,v,s}\{\sup_{\Omega_T} c_{l,D}(t,x), \sup_\Omega c_l^0(x), \sup_{\hat\Lambda}\hat c^0(\hat x), \sup_{\hat\Lambda}\hat c_s^0(\hat x)\}$, as test functions in (12)-(13) we obtain the non-negativity and boundedness of the solutions of the macroscopic problem. ■

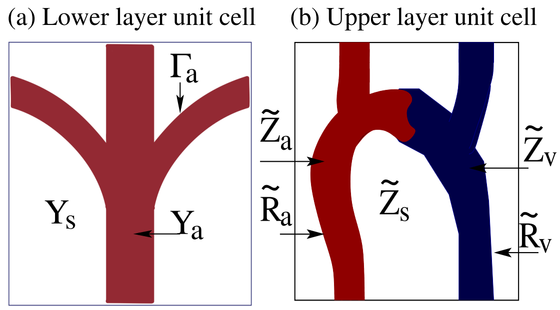

Figure 3. Two-dimensional schematic representation of the two distinct, three-dimensional unit-cell geometries used in the microscopic model: (a) unit-cell geometry corresponding to the lower layer, i.e. the fat tissue layer; (b) unit-cell geometry corresponding to the upper layer, which represents the dermic and epidermic layers of the skin. Only the arterial blood vessels are shown in the fat tissue layer.

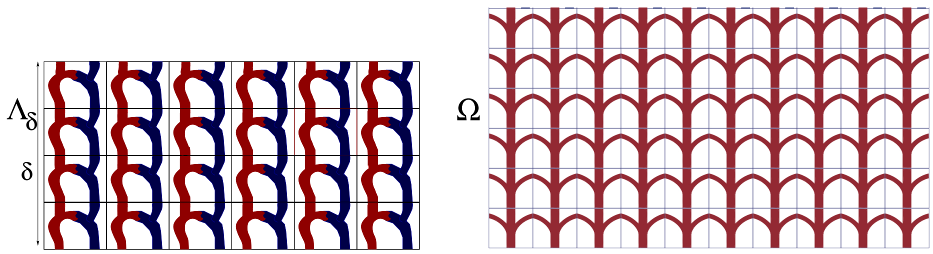

Figure 4. Two dimensional schematic representation of the three-dimensional tissue layers discussed in the text. The domain on the left (denoted by Λ^δ in the text) corresponds to the dermic and epidermic layers of the skin, whereas the domain on the right (denoted by Ω in the text) corresponds to fat tissue. Only the arterial blood vessels are shown in the fat tissue layer. Arteries (in red) and veins (in blue) are shown in the skin tissue layer, which is characterized by the presence of arterial-venous connections, i.e. geometric regions where arteries and veins meet.

8. The δ scaling for the skin layer with $0 < \varepsilon << \delta << 1$

In this final section, we consider an alternative scaling for the depth δ of the skin layer. Specifically, we assume that the adopted tissue geometry is characterized by two distinct length scales: a scale $\delta > 0$ representing the depth of the skin layer and a separate length scale $\varepsilon > 0$ characterizing the distance between arteries. In the remainder of this section, we assume that $0 < \varepsilon << \delta << 1$, and we let first $\varepsilon \to 0$ and then $\delta \to 0$. Under this scaling, the skin layer has a depth of multiple unit cells (of size ε), and we assume that the arterial branching pattern is such that flow of blood is permitted between neighboring unit cells in the skin layer.

8.1. *Derivation of macroscopic equations for velocity fields*

We first derive the macroscopic equations for the arterial and venous blood velocity fields in the two tissue layers under the scaling assumption $0 < \varepsilon << \delta << 1$. The microscopic equations for the fluid flow in the main tissue are as in (22). In the skin layer Λ_δ, $(\hat{\mathbf{v}}_a^\varepsilon, \hat{p}_a^\varepsilon)$ and $(\hat{\mathbf{v}}_v^\varepsilon, \hat{p}_v^\varepsilon)$ are assumed to satisfy

$$\begin{cases} -\varepsilon^2 \mu \, \Delta \hat{\mathbf{v}}_l^\varepsilon + \nabla \hat{p}_l^\varepsilon = 0 \, , \quad \operatorname{div} \hat{\mathbf{v}}_l^\varepsilon = 0 & \text{in } \Lambda_{l,\delta}^\varepsilon, \\ \hat{\mathbf{v}}_l^\varepsilon = 0 & \text{on } \widetilde{R}_{l,\delta}^\varepsilon \, , \end{cases} \tag{68}$$

where $l = a, v$. We impose appropriate transmission conditions on $\hat{\Lambda}$

$$\begin{cases} (-2\,\varepsilon^2 \mu\, \mathrm{S}\mathbf{v}_l^\varepsilon + p_l^\varepsilon I) \cdot \mathbf{n} = (-2\,\varepsilon^2 \mu\, \mathrm{S}\hat{\mathbf{v}}_l^\varepsilon + \hat{p}_l^\varepsilon I) \cdot \mathbf{n} & \text{on } \partial\Omega_l^\varepsilon \cap \hat{\Lambda}\ , \\ \mathbf{v}_l^\varepsilon = \dfrac{1}{\delta} \hat{\mathbf{v}}_l^\varepsilon & \text{on } \partial\Omega_l^\varepsilon \cap \hat{\Lambda}\ , \end{cases} \tag{69}$$

where $l = a, v$, along with boundary conditions (24) at the external boundaries and the continuity conditions given in (27). Moreover,

$$\hat{\mathbf{v}}_l^\varepsilon = 0 \quad \text{on } \partial\hat{\Omega} \times (0, \delta) \cap \partial\Lambda_l^\delta, \qquad \hat{\mathbf{v}}_l^\varepsilon = 0 \quad \text{on } \hat{\Omega} \times \{\delta\} \cap \partial\Lambda_l^\delta, \qquad l = a, v. \tag{70}$$

Proof of Theorem 2.3. Similarly to Section 4, we derive a priori estimates for $\mathbf{v}_l^\varepsilon$ and $\hat{\mathbf{v}}_l^\varepsilon$. To derive the macroscopic equations (15), we first consider $\phi_l(x) = \varepsilon\psi_l\left(x, \frac{x}{\varepsilon}\right)$ and $\hat{\phi}(x) = \varepsilon\hat{\psi}\left(x, \frac{x}{\varepsilon}\right)$ with $\psi_l \in C_0^\infty(\Omega, C_{\mathrm{per}}^\infty(Y))$, $\hat{\psi} \in C_0^\infty(\Lambda_\delta; C_{\mathrm{per}}^\infty(\widetilde{Z}))$, $\psi_l = 0$ on $\Omega \times \Gamma_l$, and $\hat{\psi} = 0$ on $\Lambda_\delta \times \widetilde{R}_{av}$ as test functions for the microscopic problem consisting of equations (22), (24), (27), and (68)–(70). Using the *a priori* estimates and applying the two-scale limit, we obtain that $p_a^\delta = p_a^\delta(x)$, $p_v^\delta = p_v^\delta(x)$ in Ω and $\hat{p}^\delta = \hat{p}^\delta(x)$ in Λ_δ.

Choosing now $\phi_l(x) = \psi_l\left(x, \frac{x}{\varepsilon}\right)$ and $\hat{\phi}(x) = \hat{\psi}\left(x, \frac{x}{\varepsilon}\right)$ as test functions, where $\psi_l \in C_0^\infty(\Omega, C_{\mathrm{per}}^\infty(Y))$ and $\hat{\psi} \in C_0^\infty(\Lambda_\delta; C_{\mathrm{per}}^\infty(\widetilde{Z}))$ with $\mathrm{div}_y \psi_l = 0$ and $\mathrm{div}_y \hat{\psi} = 0$, as well as $\psi_l = 0$ on $\Omega \times \Gamma_l$ and $\hat{\psi} = 0$ on $\Lambda_\delta \times \widetilde{R}_{av}$, we have

$$\begin{aligned} &\sum_{l=a,v} \frac{1}{|Y|} \Big[\langle 2\mu S_y \mathbf{v}_l^\delta, S_y \psi_l \rangle_{\Omega \times Y_l} - \langle p_l^\delta, \mathrm{div}_x \psi_l \rangle_{\Omega \times Y_l} - \frac{1}{L} \langle p_l^0, \psi_{l,n} \rangle_{\Omega \times Y_l} \Big] \\ &+ \frac{1}{\delta |\widetilde{Z}|} \Big[\langle 2\mu S_y \hat{\mathbf{v}}_{av}^\delta, S_y \hat{\psi} \rangle_{\Lambda_\delta \times \widetilde{Z}_{av}} - \langle \hat{p}^\delta, \mathrm{div}_x \hat{\psi} \rangle_{\Lambda_\delta \times \widetilde{Z}_{av}} \Big]. \end{aligned} \tag{71}$$

Using the divergence-free property of the velocity fields $\mathbf{v}_l^\varepsilon$ and $\hat{\mathbf{v}}_l^\varepsilon$, we obtain that

$$\begin{aligned} &\mathrm{div}_y \mathbf{v}_l^\delta = 0 \quad \text{in } \Omega \times Y_l, \quad \mathrm{div} \langle \mathbf{v}_l^\delta, 1 \rangle_{Y_l} = 0 \quad \text{in } \Omega, \quad l = a, v, \\ &\mathrm{div}_y \hat{\mathbf{v}}_l^\delta = 0 \quad \text{in } \Lambda_\delta \times \widetilde{Z}_l, \quad \mathrm{div} \langle \hat{\mathbf{v}}_{av}^\delta, 1 \rangle_{\widetilde{Z}_{av}} = 0 \quad \text{in } \Lambda_\delta. \end{aligned} \tag{72}$$

Then considering $\psi \in C^\infty(\overline{\Omega})$ with $\psi(x) = 0$ on $\partial\Omega \setminus \hat{\Lambda}$, and using the two-scale convergence of $\mathbf{v}_l^\varepsilon$, we have

$$0 = -\lim_{\varepsilon \to 0} \langle \mathrm{div}\, \mathbf{v}_l^\varepsilon, \psi \rangle_{\Omega_l^\varepsilon} = |Y|^{-1} \langle \mathbf{v}_l^\delta \cdot \mathbf{n}, \psi \rangle_{\hat{\Lambda} \times Y_l} - \lim_{\varepsilon \to 0} \langle \mathbf{v}_l^\varepsilon \cdot \mathbf{n}, \psi \rangle_{\hat{\Lambda} \cap \partial\Omega_l^\varepsilon}.$$

For $\hat{\psi} \in C^\infty(\overline{\Lambda}_\delta)$ with $\hat{\psi}(x) = 0$ on $\partial\Lambda_\delta \setminus \hat{\Lambda}$, and using $\hat{\mathbf{v}}_l^\varepsilon = \delta \mathbf{v}_l^\varepsilon$ on $\hat{\Lambda} \cap \partial\Omega_l^\varepsilon$, we obtain

$$\begin{aligned} \lim_{\varepsilon \to 0} \langle \mathrm{div}\, \hat{\mathbf{v}}_{av}^\varepsilon, \hat{\psi} \rangle_{\Lambda_{av,\delta}^\varepsilon} &= \lim_{\varepsilon \to 0} \Big[\langle \delta \mathbf{v}_a^\varepsilon \cdot \mathbf{n}, \hat{\psi} \rangle_{\partial\Omega_a^\varepsilon \cap \hat{\Lambda}} + \langle \delta \mathbf{v}_v^\varepsilon \cdot \mathbf{n}, \hat{\psi} \rangle_{\partial\Omega_v^\varepsilon \cap \hat{\Lambda}} - \langle \hat{\mathbf{v}}_{av}^\varepsilon, \nabla \hat{\psi} \rangle_{\Lambda_{av,\delta}^\varepsilon} \Big] \\ &= \langle \delta |Y|^{-1} \mathbf{v}_a^\delta \cdot \mathbf{n}, \hat{\psi} \rangle_{\hat{\Lambda} \times Y_a} + \langle \delta |Y|^{-1} \mathbf{v}_v^\delta \cdot \mathbf{n}, \hat{\psi} \rangle_{\hat{\Lambda} \times Y_v} - \langle |\widetilde{Z}|^{-1} \hat{\mathbf{v}}_{av}^\delta \cdot \mathbf{n}, \hat{\psi} \rangle_{\hat{\Lambda} \times \widetilde{Z}_{av}} = 0. \end{aligned}$$

Considering $\psi \in C^\infty(\overline{\Omega})$ and $\hat{\psi} \in C^\infty(\overline{\Lambda}_\delta)$ with $\psi(x) = 0$, $\hat{\psi}(x) = 0$ on $\hat{\Lambda}$ and $\psi(x) = 0$ on Γ_D, and applying the divergence-free property of velocity fields and the boundary conditions we obtain that

$$\langle \mathbf{v}_l, 1\rangle_{Y_l} \cdot \mathbf{n} = 0 \text{ on } \partial\hat{\Omega} \times (-L, 0), \quad \langle \hat{\mathbf{v}}_{av}, 1\rangle_{\widetilde{Z}_{av}} \cdot \mathbf{n} = 0 \text{ on } \partial\hat{\Omega} \times (0, \delta) \cup \hat{\Omega} \times \{\delta\}.$$

By applying integration by parts in (71), and employing the fact that the divergence-free space is orthogonal to the space of gradients of functions, we obtain (in the same maner as in section 6) the macroscopic model

$$\begin{aligned}
& -\mu\Delta_y \mathbf{v}_l^\delta + \nabla p_l^\delta + \nabla_y p_l^{1,\delta} = 0, && \operatorname{div}_y \mathbf{v}_l^\delta = 0 && \text{in } \Omega \times Y_l, \\
& -\mu\Delta_y \hat{\mathbf{v}}_{av}^\delta + \nabla \hat{p}^\delta + \nabla_y \hat{p}_{av}^{1,\delta} = 0, && \operatorname{div}_y \hat{\mathbf{v}}_{av}^\delta = 0 && \text{in } \Lambda_\delta \times \widetilde{Z}_{av}, \\
& \mathbf{v}_l^\delta = 0 \qquad \text{on } \quad \Omega \times \Gamma_l, && \hat{\mathbf{v}}_{av}^\delta = 0 && \text{on } \Lambda_\delta \times \widetilde{R}_{av,\delta} \\
& \frac{1}{|Y|}\sum_{l=a,v} \langle \mathbf{v}_l^\delta, 1\rangle_{Y_l} \cdot \mathbf{n} = \frac{1}{\delta|\widetilde{Z}|}\langle \hat{\mathbf{v}}_{av}^\delta, 1\rangle_{\widetilde{Z}_{av}} \cdot \mathbf{n}, && p_l^\delta = \hat{p}^\delta && \text{on } \hat{\Lambda}, \\
& \langle \mathbf{v}_l^\delta \cdot \mathbf{n}, 1\rangle_{Y_l} = 0 \qquad \text{on} \quad \partial\Omega \setminus (\Gamma_D \cup \hat{\Lambda}), && p_l^\delta = p_l^0 && \text{on } \Gamma_D, \\
& \langle \hat{\mathbf{v}}_{av}^\delta \cdot \mathbf{n}, 1\rangle_{\widetilde{Z}_{av}} = 0 \quad \text{on} \quad \partial\Lambda_\delta \setminus \hat{\Lambda}, \\
& \mathbf{v}_l^\delta,\ p_l^{1,\delta} \qquad Y-\text{periodic}, && \hat{\mathbf{v}}_{av}^\delta,\ \hat{p}_{av}^{1,\delta} && \widetilde{Z}-\text{periodic},
\end{aligned} \tag{73}$$

where $p_l^{1,\delta} \in L^2(\Omega; L^2(Y_l)/\mathbb{R})$, $\hat{p}_{av}^{1,\delta} \in L^2(\Lambda_\delta; L^2(\widetilde{Z}_{av})/\mathbb{R})$, and $l = a, v$. We now consider the ansatz

$$\mathbf{v}_l^\delta(x,y) = -\sum_{i=1}^n \partial_{x_i} p_l^\delta(x)\, \omega_l^i(y), \qquad p_l^{1,\delta}(x,y) = -\sum_{i=1}^n \partial_{x_i} p_l^\delta(x)\, \pi_l^i(y),$$

$$\hat{\mathbf{v}}_{av}^\delta(x,y) = -\sum_{i=1}^n \partial_{x_i} \hat{p}^\delta(x)\, \widetilde{\omega}^i(y), \qquad \hat{p}_{av}^{1,\delta}(x,y) = -\sum_{i=1}^n \partial_{x_i} \hat{p}^\delta(x)\, \widetilde{\pi}^i(y),$$

where $l = a, v$, and (ω_l^i, π_l^i) and $(\widetilde{\omega}^i, \widetilde{\pi}^i)$ are solutions of the unit cell problems (2) and (8). Using these along with (73) and (72) we obtain the macroscopic equations in (15), where $\overline{\mathbf{v}}_l^\delta(\cdot) = |Y|^{-1}\int_{Y_l} \mathbf{v}_l^\delta(\cdot, y)dy$ and $\widetilde{\mathbf{v}}_{av}^\delta(\cdot) = |\widetilde{Z}|^{-1}\int_{\widetilde{Z}_{av}} \hat{\mathbf{v}}_{av}^\delta(\cdot, y)dy$.

We remark that similar results have been obtained in [19]. We also note that the Dirichlet boundary conditions on Γ_D ensure the uniqueness of the solution of problem (15). ■

Proof of Theorem 2.5. We rewrite the equations in (15) in weak form:

$$\langle \mathcal{K}_a \nabla p_a^\delta, \nabla\phi_a\rangle_\Omega + \langle \mathcal{K}_v \nabla p_v^\delta, \nabla\phi_v\rangle_\Omega + \frac{1}{\delta}\langle \widetilde{\mathcal{K}} \nabla \hat{p}^\delta, \nabla\hat{\phi}\rangle_{\Lambda_\delta} = 0 \tag{74}$$

for $\phi_l \in W(\Omega)$, $\hat{\phi} \in H^1(\Lambda_\delta)$ and $\phi(x) = \hat{\phi}(x)$ for a.a. $x \in \hat{\Lambda}$. Considering $p_l^\delta + \frac{x_n}{L} p_l^0$ and $\hat{p}^\delta$ as test functions in (74), and using the continuity condition $p_l^\delta = \hat{p}^\delta$ on $\hat{\Lambda}$, we obtain

$$\|p_l^\delta\|_{H^1(\Omega)} \le C, \quad \frac{1}{\delta}\|\hat{p}^\delta\|_{H^1(\Lambda_\delta)} \le C.$$

Hence, considering $\tilde{p}^\delta(\hat{x}, y_n) = \hat{p}^\delta(\hat{x}, \delta y_n)$, we obtain that

$$\|\tilde{p}^\delta\|_{L^2(\hat{\Lambda}\times(0,1))} \leq C, \quad \|\nabla_{\hat{x}}\tilde{p}^\delta\|_{L^2(\hat{\Lambda}\times(0,1))} \leq C, \quad \|\nabla_{y_n}\tilde{p}^\delta\|_{L^2(\hat{\Lambda}\times(0,1))} \leq C\delta,$$

and there exist subsequences, denoted again by p_l^δ and $\tilde{p}^\delta$, and functions $p_l \in H^1(\Omega)$, $\hat{p} \in H^1(\hat{\Lambda} \times (0,1))$, $\hat{p}^1 \in L^2(\hat{\Lambda}; H^1(0,1))$, with $\hat{p}$ being constant in x_n, such that

$$p_l^\delta \rightharpoonup p_l \ \text{ in } \ H^1(\Omega), \ \ \tilde{p}^\delta \rightharpoonup \hat{p}, \ \nabla_{\hat{x}}\tilde{p}^\delta \rightharpoonup \nabla_{\hat{x}}\hat{p}, \ \delta^{-1}\partial_{y_n}\tilde{p}^\delta \rightharpoonup \partial_{y_n}\hat{p}^1 \ \text{ in } \ L^2(\hat{\Lambda} \times (0,1)).$$

The continuity of pressures implies the boundary conditions for p_a and p_v in (19). Considering $\phi_l \in C_0^\infty(\Omega)$ and $\hat{\phi} = 0$ as test functions in (74), and using the weak convergence of p_l^δ, where $l = a, v$, we obtain the equations for p_a and p_v in (19).

We now consider the test functions $\phi_l \in C^\infty(\overline{\Omega}) \cap W(\Omega)$ and $\hat{\phi}(x) = \hat{\phi}_1(\hat{x}) + \delta\hat{\phi}_2(\hat{x}, x_n/\delta)$ with $\hat{\phi}_1 \in C^\infty(\overline{\hat{\Lambda}})$, $\hat{\phi}_2 \in C_0^\infty(\hat{\Lambda} \times (0,1))$ and $\phi_l(x) = \hat{\phi}_1(\hat{x})$ on $\hat{\Lambda}$. Using these in (74) and taking the limit as $\delta \to 0$ we obtain

$$\sum_{l=a,v} \langle \mathcal{K}_l \nabla p_l \cdot \mathbf{n}, \hat{\phi}_1 \rangle_{\hat{\Lambda}} + \langle \widetilde{\mathcal{K}}(\nabla_{\hat{x}}\hat{p} + \partial_{y_n}\hat{p}^1\mathbf{e}_n), \nabla_{\hat{x}}\hat{\phi}_1 + \partial_{y_n}\hat{\phi}_2\mathbf{e}_n \rangle_{\hat{\Lambda}\times(0,1)} = 0.$$

Taking $\hat{\phi}_1 = 0$ and using the fact that $\widetilde{\mathcal{K}}$ does not depend on y_n imply that $\hat{p}^1$ is constant with respect to y_n. Finally, by considering first $\hat{\phi}_1 \in C_0^\infty(\hat{\Lambda})$ and then $\hat{\phi}_1 \in C^\infty(\overline{\hat{\Lambda}})$, we derive the macroscopic equation and boundary conditions for $\hat{p}$ in (19). ■

8.2. *Derivation of macroscopic equations for oxygen concentrations*

We now turn our attention to the oxygen concentrations in arterial blood, venous blood, and tissue, under the scaling assumption $0 < \varepsilon << \delta << 1$ that was delineated in section 8. Theorem 2.4 provides the macroscopic equations for these quantities as $\varepsilon \to 0$ while keeping δ fixed.

We consider the same microscopic equations as in (28)–(35) with the scaling $1/\delta$ instead of $1/\varepsilon$ in the transmission conditions (33). Also, for the initial data, we assume that $\delta^{-1}\|\hat{c}_l^{\delta,0}\|^2_{H^2(\Lambda_\delta)} + \|\hat{c}_l^{\delta,0}\|_{L^\infty(\Lambda_\delta)} \leq C$ instead of the corresponding assumption on the $H^2(\Lambda^\varepsilon)$ and $L^\infty(\Lambda^\varepsilon)$-norms.

Proof of Theorem 2.4. Similarly to Lemma 5.1 in Section 5 we can prove *a priori* estimates and convergence results for c_l^ε and $\hat{c}_l^\varepsilon$, where $l = a, v, s$. We consider $\psi_l^\varepsilon(t,x) = \phi_l^1(t,x) + \varepsilon\phi_l^2(t,x,x/\varepsilon)$ and $\hat{\psi}^\varepsilon(t,x) = \hat{\phi}_1(t,x) + \varepsilon\hat{\phi}_2(t,x,x/\varepsilon)$, with $\phi_l^1 \in C^\infty(\overline{\Omega}_T) \cap L^2(0,T; W(\Omega))$, $\phi_l^2 \in C_0^\infty(\Omega_T, C_{\text{per}}^\infty(Y))$, $\hat{\phi}_1 \in C^\infty(\overline{\Lambda}_{\delta,T})$, and $\hat{\phi}_2 \in C_0^\infty(\Lambda_{\delta,T}, C_{\text{per}}^\infty(\widetilde{Z}))$, as test functions in (37) and (38). Similarly to the proof of Theorem 2.2, using the convergence of $\mathcal{T}_\varepsilon^*(c_l^\varepsilon)$ and $\mathcal{T}_\varepsilon^*(\hat{c}_j^\varepsilon)$, along with the two-scale convergence of $\mathbf{v}_l^\varepsilon$ and $\hat{\mathbf{v}}_l^\varepsilon$, and letting $\varepsilon \to 0$ yield

$$\frac{1}{|Y|}\sum_{l=a,v}\langle \partial_t c_l^\delta, \phi_l^1\rangle_{\Omega_T\times Y_l} + \langle D_l(y)(\nabla c_l^\delta + \nabla_y c_l^{1,\delta}) - \mathbf{v}_l^\delta c_l^\delta, \nabla\phi_l^1 + \nabla_y \phi_l^2\rangle_{\Omega_T\times Y_l}$$

$$+\frac{1}{\delta}\frac{1}{|\widetilde{Z}|}\Big[\langle \partial_t \hat{c}_{av}^\delta, \hat{\phi}_1\rangle_{\Lambda_{\delta,T}\times \widetilde{Z}_{av}} + \langle \hat{D}_{av}(y)(\nabla \hat{c}_{av}^\delta + \nabla_y \hat{c}_{av}^{1,\delta}) - \hat{\mathbf{v}}_{av}^\delta \hat{c}_{av}^\delta, \nabla\hat{\phi}_1 + \nabla_y \hat{\phi}_2\rangle_{\Lambda_{\delta,T}\times \widetilde{Z}_{av}}\Big]$$

$$= \frac{1}{|Y|}\sum_{l=a,v}\langle \lambda_l(c_s^\delta - c_l^\delta), \phi_l^1\rangle_{\Omega_T\times\Gamma_l} + \frac{1}{\delta}\frac{1}{|\widetilde{Z}|}\sum_{l=a,v}\langle \lambda_l(\hat{c}_s^\delta - \hat{c}_{av}^\delta), \hat{\phi}_1\rangle_{\Lambda_{\delta,T}\times\widetilde{R}_l}.$$

In order to derive the macroscopic model (16) we proceed in a similar way as in the proof of Theorem 2.2. Choosing first $\phi_l^1 = 0$ and $\hat{\phi}_1 = 0$ and applying the divergence-free property and the boundary conditions for the velocity fields we obtain

$$\begin{aligned}
&\langle D_l(y)(\nabla c_l^\delta + \nabla_y c_l^{1,\delta}), \nabla_y \phi_l^2\rangle_{\Omega_T\times Y_l} = 0, \qquad l = a, v,\\
&\frac{1}{\delta}\langle \hat{D}_{av}(y)(\nabla \hat{c}_{av}^\delta + \nabla_y \hat{c}_{av}^{1,\delta}), \nabla_y \hat{\phi}_2\rangle_{\Lambda_{\delta,T}\times\widetilde{Z}_{av}} = 0.
\end{aligned}$$

Then we consider the ansatz

$$c_l^1(t,x,y) = \sum_{j=1}^n \partial_{x_j} c_l(t,x) w_l^j(y) \quad \text{and} \quad \hat{c}_{av}^1(t,x,y) = \sum_{j=1}^n \partial_{x_j}\hat{c}(t,x)\widetilde{w}_{av}^j(y)\,,$$

where w_l^j and $\widetilde{w}_{av}^j$ are solutions of the unit cell problems (5) and (9), and we take $\phi_l^2 = 0$ and $\hat{\phi}_2 = 0$ to arrive at the macroscopic equations (16).

The macroscopic equations (17) for the oxygen concentration in tissue are derived in a similar manner. Standard arguments pertaining to the difference of two solutions imply the uniqueness of the solutions of the macroscopic model consisting of equations (16) and (17). ∎

Proof of Theorem 2.6. Similarly to Lemma 5.1 we can derive *a priori* estimates for c_l^δ and $\hat{c}_m^\delta$,

$$\begin{aligned}
&\|c_l^\delta\|_{L^\infty(0,T;H^1(\Omega))} + \frac{1}{\delta}\|\hat{c}_m^\delta\|_{L^\infty(0,T;H^1(\Lambda_\delta))} \le C,\\
&\|\tilde{c}_m^\delta\|_{L^2(\Lambda_T^1)} + \|\nabla_{\hat{x}}\tilde{c}_m^\delta\|_{L^2(\Lambda_T^1)} \le C, \qquad \|\nabla_{y_n}\tilde{c}_m^\delta\|_{L^2(\Lambda_T^1)} \le C\delta,\\
&\|\partial_t c_l^\delta\|_{L^2(\Omega_T)} + \frac{1}{\delta}\|\partial_t \hat{c}_m^\delta\|_{L^2(\Lambda_{\delta,T})} + \|\partial_t \tilde{c}_m^\delta\|_{L^2(\Lambda_T^1)} \le C
\end{aligned} \tag{75}$$

for $l = a, v, s,\ m = av, s$, where $\tilde{c}_m^\delta(t,\hat{x},y_n) = \hat{c}_m^\delta(t,\hat{x},\delta y_n)$, $\Lambda_T^1 = \hat{\Omega}\times(0,1)\times(0,T)$, and the constant C is independent of δ. Thus there exist functions $c_l \in L^2(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega))$, $\hat{c}_m \in L^2(0,T;H^1(\Lambda^1)) \cap H^1(0,T;L^2(\Lambda^1))$, and

$\hat{c}_m^1 \in L^2(\hat{\Lambda}_T; H^1(0,1))$, with $\hat{c}_m$ being independent of x_n, such that

$$\begin{aligned}
& c_l^\delta \rightharpoonup c_l && \text{in } L^2(0,T;H^1(\Omega)), && \partial_t c_l^\delta \rightharpoonup \partial_t c_l && \text{in } L^2(\Omega_T), \\
& \tilde{c}_m^\delta \rightharpoonup \hat{c}_m && \text{in } L^2(0,T;H^1(\Lambda^1)), && \partial_t \tilde{c}_m^\delta \rightharpoonup \partial_t \hat{c}_m && \text{in } L^2(\Lambda_T^1), \\
& c_l^\delta \to c_l && \text{in } L^2(\Omega_T), && \tilde{c}_m^\delta \to \hat{c}_m && \text{in } L^2(\Lambda_T^1), \\
& \delta^{-1}\partial_{y_n}\tilde{c}_m^\delta \rightharpoonup \partial_{y_n}\hat{c}_m^1 && \text{in } L^2(\Lambda_T^1),
\end{aligned} \tag{76}$$

where $l = a, v, s$ and $m = av, s$. Finally, we use test functions

(a) $\phi_l \in C_0^\infty(\Omega_T)$ and $\hat{\phi} = 0$, and
(b) $\phi_l \in C^\infty(\overline{\Omega}_T)$, $\hat{\phi}(t,x) = \hat{\phi}_1(t,\hat{x}) + \delta\hat{\phi}_2(t,\hat{x},x_n/\delta)$, with $\hat{\phi}_1 \in C_0^\infty(\hat{\Lambda}_T)$, $\hat{\phi}_2 \in C_0^\infty(\hat{\Lambda}_T \times (0,1))$, and $\phi_l(t,x) = \hat{\phi}_1(t,x)$ on $\hat{\Lambda}_T$

in that order. In the same way as in the proof of Theorem 2.5, using the convergence results in (76), along with the convergence of $\overline{\mathbf{v}}_l^\delta$ and $\widetilde{\mathbf{v}}_{av}^\delta$ (ensured by the convergence of ∇p_l^δ and $\nabla \hat{p}^\delta$), taking the limit as $\delta \to 0$, and applying the fact that $\widetilde{\mathcal{A}}_m$ are independent of y_n, we obtain the limit equations in (20) and (21). The continuity conditions for c_l^δ and $\hat{c}_j^\delta$ on $\hat{\Lambda}_T$ ensure the continuity conditions for the limit functions c_l, $\hat{c}_j$ for $l = a, v, s$, $j = av, s$. The assumptions on the initial data ensure the existence of $\hat{c}^0, \hat{c}_s^0 \in H^1(\hat{\Lambda})$ such that $\hat{c}^{0,\delta}(\hat{x}, \delta y_n) \to \hat{c}^0(\hat{x})$ and $\hat{c}_s^{0,\delta}(\hat{x}, \delta y_n) \to \hat{c}_s^0(\hat{x})$ in $L^2(\hat{\Lambda} \times (0,1))$. Then, using the convergence of $\partial_t c_l^\delta$ and $\partial_t \tilde{c}_m^\delta$, we obtain that the initial conditions for c_l and $\hat{c}_m$ are satisfied. Standard arguments imply the uniqueness of the solution of the macroscopic model consisting of equations (20) and (21). ∎

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